MEETING

BEFORE THE

SCIENTIFIC REVIEW PANEL

OF THE

CALIFORNIA AIR RESOURCES BOARD

MARIAN MINER COOK ATHENAEUM

385 EAST EIGHTH STREET

CLAREMONT, CALIFORNIA

WEDNESDAY, NOVEMBER 17, 1999

9:44 a.m.

Kathleen Knowlton, CSR

License No. 11595

MEMBERS PRESENT

Dr. John Froines, Chairman

Dr. Stanton Glantz

Dr. Craig Byus

Dr. Roger Atkinson

Dr. Anthony Fucaloro

Dr. Paul Blanc

Dr. Hanspeter Witschi

Others Present:

Jim Behrmann, ARB

Peter Mathews, ARB

Paul Helliker, DPR

Randall Segawa, DPR

Dr. Gary T. Patterson, DPR

Lynton Baker, ARB

Pamela C. Wales, DPR

Dr. Thomas Thongsinthusak, DPR

Dr. Andrew G. Salmon, CEPA

Dr.Martha Sandy, CEPA

Dr. Melanie Marty, CEPA

Dr. Andrew Rubin, DPR

Dr. James F. Collins, CEPA

I N D E X

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PROCEEDINGS

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CHAIRMAN FROINES: Shall we call the meeting to order? We have a quorum. One person who will be missing today, oh, is -- Peter Kennedy is unable to come because of a health problem. But Gary Friedman, I assume, is going to be here? Gary Friedman and Peter Kennedy will not be here.

The first thing I'd like to do on the agenda is introduce the panel to Paul Helliker who's the director of -- the new director of the Department of Pesticide Regulation. And so I ask Paul to say a few words. But we welcome you, appreciate your coming to the meeting, and look forward to be working with you.

MR. HELLIKER: Thank you. It's a pleasure to be here. I assume this is the right spot to speak from. I apologize for not having been able to participate in the Scientific Review Panel meetings to date, but I'm glad that I'm able to be here today, since I've been able to review the draft findings that you've made, and look forward to having a final document from you about the workshops we've been having.

But let me just give you a little bit of background. I have a -- an opportunity to meet with Dr. Froines early on in my tenure and pointed out to him,

I think we've been marking some good progress over the past year, and I want to see that progress continue in getting a good collaborative, working relationship going with the Scientific Review Panel.

And I think that's going to set a good foundation for how we go forward with responding to the recommendations you have with what sort of prioritization plans that we implement at the department for bringing additional compounds to your attention.

So I think part of the background that has generated some of the controversy might be when we evaluate pesticides, we have the ability to move fairly quickly, and we have in the past. So I think that might have been some of the source of the discussion or the difference in approach that we have with ARB.

But my goal is to make sure that we go through the similar process to what the Air Resources Board does, and make sure that all of our decisions about toxic air contaminants are decisions that merit by the input from this panel.

Because I look to you as being one of our primary guiding organizations when it comes to our scientific decisions. So I won't take much more time than that. But look forward to the discussions today. And I did want to point out I did sign yesterday the

recommendation or the decision to list methyl parathion as a toxic air contaminant. So thank you for your recommendations on that. And I look forward to the additional ones in the future.

CHAIRMAN FROINES: Thank you. Everyone has a new record. That's great. Just great. And thank you, Craig Byus, for the effort that went into methyl parathion. I think that is, Paul, a good example of interaction. Craig and Ruby Reed worked very closely and worked very effectively. And I think that Craig is a real advocate for Ruby. And so that -- that seems to me to be a great model for how we can work effectively together.

So without further ado, we're going to -- we have -- the problem we have today is a problem we have normally. It's with Stan. I'm not supposed to make jokes, because he makes them back. But we'll cool it.

DR. GLANTZ: Let the record indicate that Dr. Froines made me get up very early this morning to get here. Actually, the problem is with Dr. Froines.

CHAIRMAN FROINES: Stan actually has to leave early. And so we are going to try and move relatively quickly, so we can at least get through item 3 before he leaves. He's finished item 4 from his compound. So -- so we have some tension about working through items 1 through 3.

Any case, so the first item on the agenda is the case study of multiple pesticides sampling. And I don't know who's presenting. This is, in essence, a continuation of a workshop on prioritization and exposure monitoring. So this will complete that small workshop.

MR. SEGAWA: Good morning. I am Randy Segawa. Yeah. We're trying to get the lights fixed there. I'm Randy Segawa with Department of Pesticide Regulation. And this is a -- pretty much a continuation of a workshop we had a couple months ago that got cut short. And I will be presenting some case studies or hypothetical examples on how we could possibly monitor for multiple chemicals.

First off, I'd like to point out that this is a hypothetical exercise. Department of Pesticide Regulation and the Air Resources Board have had a series of meetings to discuss the different alternatives and options for monitoring multiple chemicals, but we haven't settled on a concrete plan yet. So right now we're just still in the discussion stage.

For this particular exercise, I put a couple limitations on -- on how we might accomplish this. One, I -- for this exercise, I wanted to come up with some sort of objective criteria for grouping and prioritizing the different chemicals that we might be monitoring.

The other restriction I had placed on it, is that I set up the examples so they fit within the current resources available to DPR and the Air Resources Board. And the other factor I consider -- or did not consider, actually, is the risk assessment and mitigation. Those factors did not play any role in determining the groupings and priorities that I'll be discussing.

I'm going to present three separate examples on how we might group for multiple chemicals. And the first example I'll look at a crop-type grouping using cotton as an example. In this second example, I've done a chemical-family-type grouping using organophosphates as an example.

And then finally I'll present a county or month-type group where we've looked at the highest county and highest month for the various counts of pesticides and group them together. For this exercise I've included 157 pesticides, both candidate toxic air contaminants as well as those chemicals currently on the toxic air contaminant list.

I've used our current priority system, DPR's report 9601, which was published back in '96. And so is somewhat outdated, but we are working to revise that. But for this exercise, I've used that for all the candidate scores. And then for those chemicals that are

currently toxic air contaminants, I assigned an arbitrary score of 15.

A lot of this exercise, the priorities have to do with the pesticide-use data. And I've used the 1996 through 1998 data for these examples. So for each of the 157 chemicals that we want to try and monitor for, I've selected four different factors. I've looked at the crop of highest use for each of a hundred fifty-seven. We determined the chemical family each of the hundred fifty-seven belonged to.

From the pesticide-use data, we determined the county of highest use for each of the hundred and fifty-seven. And we've also determined the month of highest use for each of the hundred and fifty-seven.

So our first example, the crop grouping -- what we've done is taken, for each of the 157 chemicals, the highest crop for each of those chemicals. And cotton actually came out on top where 23 of the chemicals had the highest use on cotton. Structural pest control was second with 14 chemicals at highest use for that particular site. And then almonds was number three.

DR. GLANTZ: Structural pest control is like termites and things like that?

MR. SEGAWA: Correct. Yes. And so if you look at the list of chemicals there, there are 23 that are

used on cotton, used throughout, mainly, the Central Valley. You see that Fresno and Kern County are probably the highest for virtually all those chemicals, which you expect, since those are the largest cotton-growing areas in the state.

DR. BYUS: Are they -- pardon me. Are -- you're not saying that 23 are used on -- all 23 are used on one cotton field, are you?

MR. SEGAWA: No.

DR. BYUS: You're just saying between all the cotton?

MR. SEGAWA: Correct. Correct. Yes.

CHAIRMAN FROINES: One other question --

DR. BLANC: But your house did have 14 chemicals applied prior to your purchase.

CHAIRMAN FROINES: And xylene you have listed as a pesticide. Is that considered a pesticide on cotton?

MR. SEGAWA: It's both considered an active ingredient as well as an inert ingredient in many products.

DR. FUCALORO: Solvent?

MR. SEGAWA: Correct.

DR. BLANC: Why would it be considered an active ingredient if it's a solvent? Because it has

health effects, but not because it has pesticidal --

MR. SEGAWA: It does have some pesticidal effects for cotton. I'm not sure exactly what pest they are trying to get with xylene.

DR. BLANC: But actually, I guess I should ask the question more clearly. Because, do you know from a regulatory point of view, is a toxic additive to a pesticide which is not pesticidal considered inert? Does the term "inert" designate a non-pesticidal component or does it imply nontoxic component?

MR. SEGAWA: It implies non-pesticidal component.

DR. BLANC: So theoretically an insert ingredient can still be toxic to humans?

MR. SEGAWA: Correct.

CHAIRMAN FROINES: I was on a National Academy of Science Committee that actually discussed this issue. And you find there are a lot of compounds listed as inert that are by no means inert. And that's a problem at some level that hasn't received attention, although there has been some focus on it at some points.

DR. BLANC: And a follow-up to that question. Do you know whether inert -- other inert -- well, do you know whether there are other solvents which are considered inert? It seems that xylene is not

considered inert. That would reason I ask specifically about solvents, because of their volatility, clearly they would be of interest to this panel as potentially toxic air pollutants.

MR. SEGAWA: If I understand your question correctly, yes, there are solvents which we may consider toxic. But our list is as inert ingredients in pesticidal products.

CHAIRMAN FROINES: He's asking a different question.

DR. BLANC: I'm asking, how -- would we end up ever hearing about them at this panel? For example, suppose there was a hypothetical pesticide that was very widely used, which had a significant inert percentage of the solvent dioxane, theoretically. Would that be something that would ever enter into our inventories? Or we ever hear about or that would appear in the -- otherwise on our radar screen?

MR. SEGAWA: I'm not real sure. I know that under some of our regulatory authority -- for instance, our groundwater program, we do have the authority to look at inert ingredients as potential groundwater contaminants. I'm not sure we have the same authority for toxic air contaminants.

DR. BLANC: Can somebody from the ARB

comment on that?

MR. BAKER: I didn't hear the question. I'm sorry.

CHAIRMAN FROINES: Paul is asking the question, there are compounds that are listed as active ingredients and inactive ingredients. There are times when the inactive ingredients are toxic. And if they're volatile, that has potential significance for the designation of those compounds as toxic air contaminants.

And the question is, would that ever come before this panel? And he's, I think, not entirely sure. I think that -- and so the reason ARB comes into it is because, if there was an inert volatile compound that might be considered a toxic air contaminant, then that might come -- well, ARB, I think, 1807 lists pesticides, and that would be the role of DPR.

So I think their authority would be -- with respect to DPR would be with respect to pesticides. But inert ingredients might be with ARB. I don't know. That's the question.

MR. BAKER: This is Lyn Baker from the Air Resources Board. I would assume that solvents are carriers that might -- might fall under this category that would be toxic, but would not be pesticidal -- would not have pesticidal activity.

That the Air Resources Board might look at compounds like that under our toxic air contaminant process, but not as carriers for pesticides. If they were solvents, we would probably be viewing them from industrial sources, and might have regulated in that way rather than as a -- as an inert, pesticidal ingredient. Jeannette, would that --

MS. BROOKS: That's correct.

DR. BLANC: But let's say a pesticide came before this panel in the process that we were embarking on. And we're going to come back to this subject later. But let's take our grouped --

Suppose that our suggestion to group the cholinesterase inhibiting -- suppose our proposal to group the cholinesterase-inhibiting organophosphate pesticides goes forward and we receive risk assessment on 35 organophosphates. Are we going to be assured that as they are marketed, none of those organophosphate pesticides perforce also include volatile, toxic-air-contaminant solvent carriers?

Because if something is marketed in a particular way, which means that when it's used there will be release of a toxic air contaminant solvent then we should -- I would assume it would be our obligation to designate that pesticide a toxic air contaminant, even if

it's not on the basis of its active pesticidal component. But rather on the basis of its inert solvent carrier, unless it's reformulated to exclude that solvent carrier.

MR. BAKER: That would certainly make sense, Dr. Blanc. But the Air Resources Board doesn't have regulatory authority over pesticides. So to -- we would not have the authority to regulate or to --

DR. FUCALORO: Is there any group, I mean, within the state that is looking -- is this slipping through the cracks, I guess is what Dr. Blanc is referring to. That if you have a series of solvents that are used to deliver pesticides, is there anyone paying attention to those solvents?

I'm given to understand that xylene shows up on this list, because the pesticidal action rather than its use as a carrier or solvent. So between the two -- the two organizations, there anyone looking at these? I mean, that's a fair question, and maybe you can get back to us.

MS. BROOKS: Well, in the case of xylene, xylene is already listed. It's a hazardous air pollutant. So it's already a toxic air contaminant. And Melanie was reminding me, there are some other solvents that would be the same.

And the only -- at the Air Resources Board,

we do have a consumer products program where this would be the public being able to go in and buy off the shelf Raid or something like that. And we're limiting the volatile organic content of those. And a lot of the carriers are what we're regulating, trying to get as low as we can, close to zero BOC.

And we know, too, those products are labeled. If these carriers are toxic like xylene, and maybe toluene, they have to be labeled for Proposition 65. So there is at least a warning. But I know what you're saying as far as control measurement development.

DR. FUCALORO: Yeah. Clearly if a carrier were benzene, it would raise red flags all over the place. I understand that. But suppose, for example -- I'm just following up what Dr. Blanc is saying.

Suppose there is a solvent that is really not being considered in any way as no one's done any investigation of it, and a manufacturer uses a carrier that uses a solvent that no one has investigated, is there any mechanism within the state to say, this is something we ought to be looking at? I assume it's the ARB.

MS. BROOKS: Under our toxics program, in a consumer product that's sold, we can do a toxic control measure for a toxic air contaminant. And in fact, we have a branch at the board that's looking at break cleaners and

engine degreasers that contain perchloroethylene right now. And they're planning to take a control measure to the board next year.

So I think for a commercial product where the Air Resources Board has authority, we could develop a controller measure. And, in fact, we are. For a pesticide that's used on application at a farm, I don't think we could control the xylene content.

DR. GLANTZ: Could DPR?

MS. BROOKS: We have to double-check on that.

MR. BAKER: I would think that would fall to DPR.

CHAIRMAN FROINES: I'm going to cut this off, because we are way off what this session is about.

DR. BLANC: Sorry. My fault.

CHAIRMAN FROINES: No, nobody should apologize. It's a very important discussion, and we should take it up at a later date. We've now certainly raised it, and so let's leave it for the moment. I'll just, as Chair's prerogative, will say this last word on it.

DR. GLANTZ: This is part of Dr. Froines' effort to always shorten discussions.

CHAIRMAN FROINES: Under AB 1807, compound

is listed as a toxic air contaminant. The law then says that a risk-management process will follow. It doesn't say, "only for these uses, compared to these uses."

So if there is a toxic air contaminant, say xylene, then it seems to me that the issue is what is the appropriate, regulatory-management strategy that you would follow for that compound, for any and all of its uses. And so it would be up to ARB to determine those uses and to determine strategies for control.

MS. BROOKS: That's correct.

CHAIRMAN FROINES: That's, I think, what the question is. And this is obviously something that hasn't come up before, so we can talk about it later. Thanks. Thank you.

MR. SEGAWA: Okay. This figure here shows the use for all the 23 chemicals that we were just discussing. As you can see, that the San Joaquin Valley has the highest use for chemicals used on cotton. And of course, that is where most of the cotton is grown.

But you can also see that there is use of these chemicals throughout much of the state down, in the Imperial County and southeast desert region, as well as even far up north in the Modoc County area as well.

And don't forget, while these chemicals may have highest use on cotton, cotton would not be their only

use. They would also be used on other crops. Okay. Moving on to --

CHAIRMAN FROINES: Not much of those, do you think, of the 20 -- we know xylene's organophosphate. But how many of the others do you think are organophosphates?

MR. SEGAWA: Organophosphates? Phorate is an organophosphate. Chlorpyrifos, of course, methamidophos, naled, def, and ethephon.

CHAIRMAN FROINES: I only ask that question because, clearly, where you have a common mechamism of action, you would want to look at the compounds with common mechanism of actions collectively, if one were able to.

MR. SEGAWA: And that's a good segue into the next slide. Because the second example does deal with the chemical-family-type of grouping. Again, for the 157 candidate and TAC chemicals that we're looking at in this exercise, 20 of them are organophosphates. And they came out highest in the priority score in the grouping.

Organochlorines came in second. There are eight chemicals in that group. And carbamates is third with nine chemicals. And so if you look at the list here, these are all organophosphates used on variety of crops. And you can see, used at a variety of locations and throughout most of the year.

DR. ATKINSON: So it looks as though at least three of these are also organochlorines.

MR. SEGAWA: That's probably true, yes. And then as a third example, we took the 157 chemicals and determined the combination of county a month of highest use. So that if we were to try and monitor for multiple chemicals, it's, of course, ideal to be monitoring at the same time in the same place for multiple chemicals.

And in this type of grouping, Fresno in July came out as the highest -- scoring with seven chemicals in that group. Fresno in June was second with five chemicals. And Fresno in August was third with four chemicals.

And the drawback to this type of grouping, as you can see, is that the chemicals in the highest group, the Fresno in July, are different groups of chemicals. And so they would require several different sampling and analytical methods to try to get them all at the same time.

After looking through these various exercises, we came to several conclusions regarding the shortcomings and problems. Number one, it's difficult to monitor the complete groups, whichever the three groupings we chose. It requires monitoring in several different seasons, as well as several different areas, and using

several different types of monitoring methods.

While this is, maybe, a good approach for the ambient monitoring, it probably does not work for the application monitoring, since in most application monitoring, one to three chemicals would be applied at the same time, not groups of 20 or more.

And of course, risk-assessment factors have not been addressed in this exercise. And it's very likely that, to do the risk assessment for multiple chemicals, particularly outside the chemical-family grouping, would be very difficult. Any questions?

DR. FUCALORO: Yeah. I guess you were looking at some sort of intersection of these lists; is that correct?

MR. SEGAWA: Correct.

DR. FUCALORO: And looking at the monitoring multiple chemicals, county look, the month group, it seems to me that quite possible that you don't need an intersection. I missed the original pesticide workshop, so I'm a little unclear as to what's going on. But what you consider, the list under Fresno in July, probably Fresno in June and August, too, as being a candidate for multiple testing.

MR. SEGAWA: Yes, you're correct, that if we were actually to follow this type of scheme, that we would

probably be monitoring in June, July, and August, yes. And the list would expand as well, of course.

DR. FUCALORO: I'm not encouraging people to go in Fresno in June, July, and August. In fact, I would discourage them.

CHAIRMAN FROINES: I make just one comment. That list of compounds, the seven chemicals -- 1, 2, 3, 4, 5, 6, 7 -- in terms of your '96 priorities, they -- we have here the first compound the highest priority, the fifth highest priority, the seventh highest priority, the 39th highest priority, and 42nd, 58th and 63rd.

So it represents, actually, a relatively important cross section of compounds that your priority document identified. And in fact, one would say, these are all candidates that are worth taking a look at, given their priority in the DPR '96 document. Has -- has Lyn -- have you and Lyn talked about the actual analytical and sampling methodology required to look across --

MR. SEGAWA: We did ask Air Resources Board to take a quick look at these various lists and come up with a ballpark estimate as to how many methods are required, and how they would go about doing it. In this particular case for the seven chemicals in the county-month grouping, they thought it would take two or three methods.

CHAIRMAN FROINES: Two or three?

MR. SEGAWA: Yeah.

DR. BLANC: That sounds technologically feasible.

MR. SEGAWA: Uh-huh.

DR. BLANC: I think from some of this, probably be tempered by logistical considerations also. But one advantage I think you may have, given the weather and pesticide-use patterns, is that even for certain other areas outside of Fresno County that you might be interested in, the time frame when you would need to sample would be a different time of the year, thus making it, you know, physically possible for the staff to contemplate sampling.

For example, you know, there's a -- there certainly is a heavy concentration of use in -- probably in Imperial County at certain times of the year, and similarly in Salinas Valley which may differ from Central Valley.

MR. SEGAWA: I would agree, yes.

DR. BLANC: So therefore, there would be things that you -- sampling there, even if they -- they -- so I guess, another thing I would suggest, in addition to the very excellent analysis, would be an analysis where it was divided up by agricultural region, and you saw what

was the time at which the most number of chemicals were used in Imperial County. So that you leave aside the issue of, how does Imperial County rate compared to Fresno.

It's going to be clear that areas in the Central Valley are going to be the heaviest pesticide use. But there may be very real issues in some of these other geographic agricultural areas, because the types of pesticides used are likely quite different.

MR. SEGAWA: Yes. My guess that meteorological conditions would be different in those areas as well.

DR. BLANC: I would suggest that you do that analysis as well. I would like to see that analysis for three or four of what you would imagine would be key areas. And I guess, those key areas would be the North Central Valley as opposed to Fresno and Kern, Salinas Valley, Imperial, and then perhaps, based on your map here, probably certain other hot spots.

CHAIRMAN FROINES: Comments? Thank you very much. This is a really nice piece of work. And I think it just raises a lot of interesting questions. So hopefully we can pursue it over time. I think it's really well done and thought-provoking, as you can tell. Have you ever done -- never mind. I'll ask another time.

MR. SEGAWA: Okay. Thank you.

DR. GLANTZ: Can I just ask one quick question? So where are you planning to go next with this in terms of -- I mean, I agree with the others who said -- I think it's real interesting. I mean, are you going to further develop these ideas and come back again to us or work with ARB? What's the sort of next -- what's the plan over the next couple three months?

MR. SEGAWA: We can do that. We of course need additional discussions with Air Resources Board to see which approach we do want to take. If it's possible, can go with our current resources, and we can come back to the panel with a more updated recommendation.

CHAIRMAN FROINES: I should tell you, by the way, that I have a Ph.D. student who's doing a study of multiple-pesticide exposures in Mexico. She's looking at about ten pesticides, and she's doing the analytical chemistry herself.

And she's also looking at soil, water. She's doing a multi-media, multi-environment and looking at -- also at urinary metabolites, and looking at what families and children of workers and applicators are getting. So we will keep you informed of what that data looks like, because it's very parallel, in some respects.

DR. GLANTZ: Getting back to the earlier

point, though. I hope that at some reasonable time they can come back with a sort of next iteration on this.

CHAIRMAN FROINES: So we should define an action item. What's a good action item of a report in three months for this? What's a good reasonable time frame for you?

MR. SEGAWA: We can do that in three months.

CHAIRMAN FROINES: That good? Thank you.

MR. SEGAWA: Thank you.

CHAIRMAN FROINES: The second item on the agenda is the prioritization -- B and C we'll take together, is a discussion of the prioritization and air monitoring document that we wrote up.

If you'll remember -- if the panel will remember at the September meeting, Stan and Paul, in particular, recommended that the Chair write a document that could be sent to DPR with our recommendations and conclusions from the mini-workshop. And I said that I would -- wanted to have input from the panel.

So we went ahead and wrote a document which you all had for, I think, a reasonable period of time to read and review. I know we've had comments from Roger Atkinson up to this point. And what we would like here is, on a discussion with the agencies -- this is really an internal matter to the panel.

Basically what I need is for you to give us final recommendations and suggestions so we can then take this document or modified version, send it to Paul Helliker at the agency for their consideration. So I think the best way to handle this would be to go around the room and get people's comments.

DR. GLANTZ: Well, I -- I think -- I think it's basically quite good, actually. I think -- and I -- the revised draft, which I got a couple days ago, I agreed with many, but not all of the changes. Because I think that some of the changes, while perhaps toning it down a little bit and making it a little bit more palatable politically, have made it less clear.

And I just like to go through the specific things that I would suggest we -- I'm working not off the one that we were just handed, but the one that you E-mailed around. Has a red-line, strike-out format.

So if you look under part A, number 1, I actually think the original statement that prioritization for the SB50 program has overshadowed -- or no. The original thing which is shown as struck out, "DPR has not used the AB 1807 prioritization method," was -- is just clearer, I think. So I would suggest going back on that one. And the same -- let's see. I want to make sure I didn't --

DR. BLANC: How about "not appropriately used"?

DR. GLANTZ: Well, I don't think they've used it.

DR. BLANC: They may have used it in some instances. I don't know. I mean, they may have in some kind of ad hoc way. I don't know, but --

DR. GLANTZ: This was discussed endlessly over many years. And we were told over and over and over again that the SB950 program took -- was more important. Maybe if you wanted an intermediary, you could say, "DPR has used SB950 over AB 1807." But I think that's the statement of fact which is correct. And I mean, the other -- the statement --

CHAIRMAN FROINES: Stan -- Elinor, can you try -- we'll get the transcript. Can you try and write down what is being said?

DR. FANNING: Yeah. I'm, like, making notes.

DR. GLANTZ: I don't feel violently about any of these things. Let me just think here. And then number two, I think that the original statement, "Prioritization for SB950 does not necessarily reflect the likelihood of being a toxic air contaminant," is also a clearer statement than --

DR. BLANC: I'm sorry. Which one is that?

DR. GLANTZ: This is number two. I think that was a clearer statement. For number three, I have a third wording. I would say, "The process used to select pesticides for active risk assessment at DPR has not generally taken into account TAC candidate status."

CHAIRMAN FROINES: Is that --

DR. GLANTZ: That's number three. Huh?

CHAIRMAN FROINES: Did you write that?

DR. GLANTZ: Yeah.

CHAIRMAN FROINES: So you'll give that to us?

DR. GLANTZ: Yeah. I mean, these are -- and then let's see. With number five, I just had a question about that. I think that original statement, "In the past, pesticides selected for monitoring did not reflect TAC priorities," is true.

The alternative wording, that it "better reflects TAC priorities than in the past," is also true. But in the past, they didn't seem to be paying much attention to them at all, to me. So I would be a little meaner, I guess.

The number six, I think the original wording, "DPR does not routinely consider USEPA risk assessments," is a clearer statement than the thing which

has been reworded. I think that was it. Let me just look.

The other changes that were made were all fine. Oh, and then, if you go to number -- page -- what is my -- page 10, number 4, the -- where we -- it had said -- the original wording was, "DPR should supplement monitoring data," and it was changed to "could." And I prefer "should." So --

DR. FUCALORO: Just want to subtract the power of the subjective.

DR. GLANTZ: What? Whatever. I think we want to make it affirmative recommendations here. You know, because I think that one of the things that I think came out of the workshop was, you know, trying to couple -- you know, get a better job of getting a handle of what's actually going on.

And -- and so, I think we should say "should" there. But those are my -- the rest of it is fine. The rest of the changes were fine. So I don't know if you want to discuss that or just go around the table.

CHAIRMAN FROINES: I think if anybody has comments as to what your recommendations are --

DR. GLANTZ: I'm keeping Dr. Blanc awake.

DR. BLANC: I don't feel strongly about the things you said. I mean, it's fine. Only thing I would

say is, that I would defer to the Chair's discretion. If after having heard your concerns, he still chooses in certain of the instances to temper the tone of some of these things, since you're closer on the ground to the likely effectiveness of the document and how it might be impactive, depending upon specific wording.

But I think that Stan's general direction of trying to be as explicit as possible, assuming that it wouldn't be counterproductive, is a good general guideline. But you have final responsibility.

CHAIRMAN FROINES: And Paul Helliker has heard both comments. He understands that the context --

DR. BLANC: Right. I have some specific questions. On page 2, point 2 --

CHAIRMAN FROINES: Well, let's go around. Craig?

DR. BYUS: Okay. I agree with what Stan said. I'm not totally strong about it, but I think the stronger language is probably the better choice. I just would like to echo the point 2 here about considering a vast approach relisting high priority organophosphates.

I really think this is an excellent idea, considering how many organophosphates there are, and the fact that they all do work by a common mechanism. So I really think this is an excellent idea. The

possibility -- likely -- high likelihood of multiple organophosphates being used on the same crop is, in fact, likely.

So I pretty much like the document as it's written. I would like to add, though, that I think that some -- pardon me. Pardon me. That some examination or incorporation of the food residue -- we have all this data somewhere. There is somewhere a lot of data about what pesticides actually are on foods.

Now -- and so this could really be a guide for which pesticides are used together. I mean, clearly they had to be used on the same crop. Now, clearly, it wouldn't incorporate all pesticides, because some might be less stable and maybe wouldn't show up in food residue. But there's a lot of multiple-pesticide-use data in the food-residue data somewhere.

It could -- could be used to guide prioritizations for -- in terms of multiple risk for multiple pesticides, when they were applied. I tried to find out about some of that information, but I -- when I was doing methyl parathion. But it became just too cumbersome to try to do it. I do think there is a lot of information there about it -- about multiple pesticide use in the food-residue data.

CHAIRMAN FROINES: That sounds almost like

an academic research project.

DR. BYUS: It does. It does. But that's all.

CHAIRMAN FROINES: Which would be good.

DR. BYUS: Yeah. Oh, sure.

DR. ATKINSON: Well, talking -- I'd like to also echo the -- that I like the batched approach for listing of chemicals. Certainly makes sense from an environmental-type of approach, as well. Certainly organophosphates, since there isn't a lot of data, they'd be much more easily dealt with as a whole batch.

Another thing is, I'd like to -- I certainly endorse the controlled applications, that DPR should do controlled applications for site monitoring, rather than preferably to spending time and energy doing ambient monitoring.

CHAIRMAN FROINES: I think that's a very important recommendation. And I think it was made particularly clear by Bob Spear's presentation. And from the standpoint -- again, from the standpoint of identifying a compound as a toxic air contaminant, ambient monitoring has different implications for risk-management purposes. And that's also --

DR. ATKINSON: Yes.

DR. FUCALORO: As you know, I wasn't at the

September workshop. I couldn't make it. But I did read this document and noted a few things that some of you noted. The -- the monitoring -- the regulated monitoring, that was a good one. Of course grouping the organophosphates is another one.

The one thing I noted -- and I wasn't, again, part of this discussion. This is on page 9, number-one recommendation. Says, "DPR should consider basing TAC listing on application site monitoring results, and using ambient primarily in the risk-management phase." I was just wondering, if that really meant TAC priority listing or does it just mean --

DR. BLANC: I think that was the intent. I circled the same thing. Because they don't actually list something as a TAC.

DR. FUCALORO: That struck me.

DR. BLANC: We recommend that something be a TAC; right?

CHAIRMAN FROINES: Yes.

DR. BLANC: So that wording needs to be changed to be clearer. It implies that the DPR is identifying -- is from a regulatory point of view listing something as a TAC. Whereas what you're saying is how to do their listing of priorities for consideration as a TAC. Something -- I don't know that being too.

DR. FUCALORO: Well, their priority list -- I think that's become a common language with ARB and DPR, the priority list in which chemicals are used and go to next in order to see if we are going to designate them as TACs.

CHAIRMAN FROINES: Well, the -- this goes back in history to the -- to the debate that we've had with DPR since the mid '80s where we have always strongly disagreed with DPR on -- on the MOE as the basis for a TAC listing.

We've always taken the position that a compound should be designated as a toxic air contaminant based on its toxicity. And that's different than the DPR position. So that this recommendation for application site monitoring is, in essence, to -- to -- is in essence saying, if you're going to use the MOE, then we think application site monitoring is the most appropriate approach to that for purposes of identifying TACs.

DR. FUCALORO: And this highlights the difference of what I think ARB does and DPR, on the other hand. ARB will look at potency factors in some way and designate something a TAC, and then use exposure as part of mitigation; right?

Whereas DPR brings exposure in also -- exposure and potency factors, whatever they are, cancer or

noncancer effects, and then uses that as a basis for designating something a TAC. But both, organizations as far as I understand, use both of those in order to set up a priority list. I think -- I think I have -- I think I have that right.

CHAIRMAN FROINES: The problem, of course, with the ambient monitoring, leaving aside the variability issue is, you can go back to the data that is available for us to review on methyl parathion and the actual monitoring data that was available was very limited. So we ended up, I think, used Jim Seiber's data, which was one study from the '80s.

I mean, it's -- it's really, when you base major policy and scientific decisions on one study done in 1988, 1987, and that forms the basis of whether something's a TAC or not, you realize the limitations of that approach.

So if we had lots of data that dealt with variability, that's a different issue. But in any case, to the degree that we continue this approach with the MOE, then application site monitoring becomes obviously the preferred approach, at least from the standpoint of this panel. Paul?

DR. BLANC: I have a number of text changes I'll just pass on to your colleague. But let me ask you

my substantive questions. In page 2, point 2, the last line, "Further, the SB950 process does not use a quantitative ranking scheme."

CHAIRMAN FROINES: Where are you at?

DR. BLANC: The last line of section 2, on page 2, you know, "The criteria used to prioritize SB950 differ from those articulated by DPR." In that section, the last line. "Further, the SB950 process does not use a quantitative ranking scheme." I just wanted to be clear on that. Do you mean you're not referring therefore to their priority list, which did have some kind of rank?

CHAIRMAN FROINES: No. They have this committee, remember?

DR. BLANC: Right.

CHAIRMAN FROINES: And the committee basically defined the priority, and that they're not, in essence, using this document for prioritization. This is the quantitative document that effectively is not being used.

DR. BLANC: Okay. And when they -- you -- you -- I think it was a little confusing, because they -- they rank things in three groups or something; right? So it is -- it's very roughly a semi-quantitative. But it's not the -- there's no process to it. It's two separate issues to me.

And the stronger one is not that they -- not so much that they group things in the three groups, you know -- bad, very bad, and better -- but that there is no rationally articulated process by which they do that. And I thought that needed to be stated more clearly.

And I wondered, in fact, if on -- and this is the related point, I think, in terms of recommendations on page 5, where it says -- current language is -- the third point is, "Develop a policy for coordination of priorities under different programs that require DPR to prepare risk assessments for pesticide." That's getting at this process; right?

And what I would rather explicitly say, that they need to delineate explicite criteria for ranking, rather than the currently used ad hoc procedure. Because of all of the things we heard, that was, for me, the most disturbing, was that there could not -- maybe they have something. But they could not explain it to me in a way that sounded coherent.

That there was actually -- so I don't mean that they have to prepare a 500-page document. But they need to have a clearly delineated process. And I think we need to say that.

CHAIRMAN FROINES: Does everybody agree with that recommendation?

DR. BLANC: I mean, I wouldn't make it as a new point, necessarily. But I think that's the point I'm trying to get at. I also thought that -- going back earlier, back to page 2 on point 3 where it says -- the point that has to do with, "The process used to select pesticides for an active risk assessment does not necessarily take into account TAC candidate status." And I would say that the decision --

CHAIRMAN FROINES: I'm sorry. Where are you?

DR. BLANC: Point 3, on page 2. And I would say that the problem is not that they don't seem to be guided by a specific policy approach. I think they're not guided by a coherent policy. It's not the lack of specificity that bothers me so much, it's that it's incoherent.

And similarly, on point 4 on the next page, it's not that the process used to select pesticides for air monitoring has been distinct from the risk assessment, it's been disconnected from the risk assessment. I notice you use the word "disconnected" later, but I really think that that's --

On page 4, point 6. Well, after point 6. These six points summarize the information which was presented in that first part. And you get into this in

the second half. But the fact that the changing-use patterns are not incorporated in a timely fashion to priority setting, it's emphasized a lot in the sampling. But I thought it was a critical issue that came up relevant to the priority setting, as well.

Now, going on to the next section. In terms of the -- the next set of -- next set of recommendations, on the batching the organophosphate pesticides, this is a technical question -- two technical questions. One is, do we need to specify cholinesterase inhibiting organophosphates?

The reason I ask, I know there are carbamates which are not cholinesterase inhibiting and are used for other purposes. Are there any -- technical question for DPR. Are there any organophosphates which -- whose principal means of action is something other than cholinesterase inhibiting?

CHAIRMAN FROINES: Well, there is the issue of --

DR. BLANC: I'm going to get to the -- just --

DR. PATTERSON: I'm Gary Patterson from DPR. And, no. It's -- organophosphates by nature are cholinesterase inhibitors.

DR. BLANC: So unlike the carbamates, some

of which --

DR. PATTERSON: Diatomic carbamates usually are not.

DR. BLANC: Right. Okay. Fine. But I do think we may need this -- this section to say something about organophosphates with delayed neurotoxicity. Because in the batching process, we're certainly going to have to take into account whether within those organophosphates, any of them have delayed neurotoxicity. Thanks.

And I thought that point 3 is really what you really -- what we're really trying to say. They need to delineate specific criteria for ranking rather than the currently used ad hoc procedure. I think I said that already. Okay. In Dr. Spear's comments --

CHAIRMAN FROINES: What page are you on?

DR. BLANC: Page 8. Under the heading, "Ambient monitoring may not result in useful characterization of population exposure." You have here his critique of the ambient air monitoring, but not necessarily alternatives that he also suggested.

And since you've come back to that in the recommendations, invoking him. I guess, one question that I have is, aside from the comment and discussion about sampling in control applications, didn't Dr. Spear also

talk about the importance of modelling -- of theoretical modelling exposure?

CHAIRMAN FROINES: Yes.

DR. BLANC: And there's no recommendation here in -- A -- A, it's not described here. But B, there's no follow-up recommendation that says that, in addition to these other things, models of exposure should also be used in estimating.

DR. ATKINSON: Point 5, the last sentence has -- computer modelling is mentioned.

DR. BLANC: Where is that?

DR. ATKINSON: Same page.

CHAIRMAN FROINES: Last sentence of number 5. Page 8, last sentence.

DR. ATKINSON: That's just mentioned.

DR. BLANC: I'm sorry. Page 8, point 5?

CHAIRMAN FROINES: Last sentence.

DR. BLANC: Under "Currently proposed changes to the ambient monitoring program may increase the time required." Maybe -- page 8.

DR. ATKINSON: Page 8, point 5.

CHAIRMAN FROINES: Last sentence in the paragraph under 5.

DR. FUCALORO: It says -- starts with "Other ideas under consideration."

DR. BLANC: (Reading.) Well, I think you should -- I think it got lost in the shuffle, because I thought it warranted being a separate --

CHAIRMAN FROINES: Yeah, I think it could be made more explicit. Take your results of application site monitoring and use dispersion models for predicting ambient concentrations.

DR. BLANC: Okay. Those were my --

CHAIRMAN FROINES: It's all good. Everybody's fine with that? Peter?

DR. WITSCHI: Yeah. Not much to add, except I picked up on Spear's point which says, "very limited value." So first question must come to mind, why are we doing it at all? The second one comes -- comes out like Mark Twain in the weather, everybody complains about it, but nobody's really doing something.

And I think what's really missing is some overall master plan or great view of how the whole exposure assessment could be improved so that it can serve the purpose we would like things, and that's the health-risk assessment.

Because the way I've seen -- this includes this morning's presentation, that was very good. But we are going to monitor more and more without really having a clear view of what is going out to be, and for --

CHAIRMAN FROINES: Well, I think that DPR has requested that we assign a panel member or more to work with them on -- on these recommendations. And certainly the issue of exposure-assessment monitoring would be one of the question features.

Now, what I did was to propose that Elinor -- Dr. Elinor Fanning, who's working with the panel, and who has more time than the panel members to work with them. But I -- but I think that we need to assign at least one or two people to work with DPR to address precisely the kinds of questions that you're raising.

And so, if I can use your comments -- I wish Stan were in the room. We -- it would be good to have a volunteer or two to agree to work with DPR on the issues that arise out of this document. And I think that the two people who are missing are not the appropriate people for this. I think it takes people who have some more knowledge of exposure-related issues.

So I think this group here today is actually the best. And if nobody wants to volunteer, I'll just take that as -- take that silence as silence and then we'll work it out outside, you know, the lights of the meeting. Or we can assign Stan, because he's not in the room.

DR. BLANC: And he's leaving early. So he should be punished.

CHAIRMAN FROINES: So hearing no volunteers, we'll take it up after the meeting. Anyway, go ahead, Peter.

DR. WITSCHI: That's about all. I'm still puzzled. I still do not see any good way how the human data can be used for human health-risk assessment. And I also see that we are doing more and more, which is going to be less and less useful for this purpose.

CHAIRMAN FROINES: Well, this is a specific example of a major problem, as you know, about how monitoring data is used in air pollution exposure assessment. It's one of the -- it is one of the -- it is -- it is basically the first-stated priority by the National Academy of Scientists, committee on Particulate Matter. So it's a key issue.

So I think that we're finished with this. We'll take all these suggestions -- we'll take all these suggestions and develop a final document and send it off. I don't know, Paul, if there's anything that you heard this morning that makes you want to comment now or you want to just wait till you receive the actual, formal document. But it's your call.

MR. HELLIKER: My make of it is, I think

this is an excellent document, and it will help guide us as we go forward. And as you just mentioned, there are some fundamental problems that we face. And we will seek your input and your assistance in helping to make a reasonable choice as we go forward in all of our regulatory programs.

But, I appreciate this. And certainly it reflects some of my impressions, as I've come into the department, that we do need to be clearer in defining for you, as well as for other stakeholders out there, as what our processes are, that we've gone through in making decisions about the prioritization about different monitoring and different risk assessments. So I'm looking forward to responding to this.

CHAIRMAN FROINES: Thanks. Okay. Do we want to take a break? Don't you? Just for everybody, got a note from Peter that Stan was on the phone. We'll take a ten-minute break.

(Brief recess taken.)

CHAIRMAN FROINES: The next item on the agenda is MITC. This will be a staff report from DPR. The panel will not take up the document today for discussion purposes. That doesn't mean that we can't ask questions as the presentation is made. And you're welcome to do that.

But in terms of our formal -- a formal discussion of the document, that will happen at our next meeting, and we will have the benefit at that time, also, of the OEHHA comments, which we currently don't have. And we'll also have the benefit of Peter Witschi's final -- final review.

So those two things are -- because they're still outstanding, I want to not try to take it up. Also the -- before we start on MITC, I have overlooked saying something at the beginning that I want to catch up and say thank you very much to Tony Fucaloro for hosting us here.

DR. FUCALORO: Actually, the thanks goes to the staff of Athenaeum. They are very competent and very helpful. I'll transmit that thanks to them.

CHAIRMAN FROINES: If you have any comments you want to say about the history and anything else, please feel free.

DR. FUCALORO: Yeah, but I'll probably get it wrong. It's been told to me several times, and I'm not sure I have it right. But this is a product of one of our founding -- one of CMC's founders, Donald McKenna, who recalls having students and faculty together for teas and dinners at -- when he was a student at Pomona College.

So he tried to get that -- that to happen at Claremont McKenna College, and he was successful. And

under Jack Stark raised money for this -- this building, and to raise the funds to endow it.

So four nights a week, for example, we will have a something -- we'll have -- similar to what you're doing tonight, which we'll have a reception, we'll have a dinner, and then a presentation in this main hall. And students and faculty from all the colleges, whether they have meal plans or not, eat for free.

And that's all endowed. And so it's quite a program. Runs four times a week during the academic year. So it's a great facility, and it brings faculty and students together. And it's not a faculty high house -- high table as you would find at another institution. Almost all events, with the exception of a few like this one, require students' attendance and student participation. So that's pretty much the philosophy and the thinking behind this -- this program -- the Athenaeum program.

CHAIRMAN FROINES: Well, thank you again. I think it's lovely.

DR. GLANTZ: Where did the name come from?

DR. FUCALORO: Well, I was ambushed to give a history of this place, and you're asking about -- I know there's a city named Athens --

DR. GLANTZ: Okay.

DR. FUCALORO: -- that goes back to antiquity and has quit a history. But beyond that, I'm a chemist. What the heck?

DR. GLANTZ: Well, would you find out and report back at the next meeting?

DR. FUCALORO: I know there's an Athenaeum at Cal Tech -- at Cal Tech.

CHAIRMAN FROINES: This is not a graduate student's oral, and you don't keep asking them questions till you find the one he doesn't know the answer to.

DR. PATTERSON: We only do that to DPR.

CHAIRMAN FROINES: Okay. MITC.

DR. PATTERSON: Again, I'm Gary Patterson from DPR. Paul Goslyn is unable to attend this meeting, and he sends his apologies. And few statements that he wanted me to start with was, he wanted me to emphasize the importance of your input on MITC, and that it will be used to help guide us through the risk-management phase for this chemical.

In addition, he's very interested in hearing your thoughts on the sensitivity of the end points that will be presented today. And on one side note, we gave you a list of four chemicals that we were going to do for the year. We're going to replace naled with chlorpyrifos.

And with that, then, I'll turn it over to staff to make a presentation. The first person will be Pam Wales to do the environmental fate.

MS. WALES: Good morning. My name is Pam Wales. I'm with the Environmental Monitoring and Pest Management Branch at DPR. And -- next slide. I'm going to very briefly cover the valuation of MITC as a TAC on the environmental fate of this chemical.

The three points that I'm going to cover very briefly this morning are: The fate of MITC and the environment, and focusing mostly on the air; the use in California; and also cover some air monitoring to determine levels of MITC following applications.

When we talk about MITC, we're really talking about three pesticides. MITC, on the bottom of the slide, is registered in California for use as a wood preservative. Use in California is about 350 pounds per year. MITC is very volatile. Its vapor pressure is about 16 millimeters of mercury, and the Henry constant is at 1.8 times 10 to the minus 4 atmospheres, cubic meters per mole.

MITC is used to control wood decay organisms in large structural timbers. It's typically not used in crop-land setting. However, there are two other pesticides. One is called Dazomet, and the other

Metam-Sodium, for which MITC is the principal active in their formulations.

Dazomet is registered for use in California as a slimicide and biocide. It's used in cooling water treatments and also in -- just had a brain fade. Also, one product is used as a pre-plant fumigant. The use of Dazomet is about 20 thousand pounds per year, and it breaks down to form MITC.

Metam-Sodium, on the other hand, is registered for use as a pre-plant fumigant, wood preservative, and also for root control. And in California, in the agricultural setting, almost 16 million pounds are used per year. While Metam-Sodium itself is non-volatile, it does break down rapidly to MITC.

Next slide. As I've said, the primary source of MITC in the environment is from the breakdown of Metam-Sodium. Metam-Sodium is applied to a soil either by soil injection or by chemigation. It's usually --

DR. GLANTZ: What is chemigation?

MS. WALES: Chemigation is irrigation -- treatment by irrigation.

DR. GLANTZ: Does that mean put it in the irrigation water or they just spray it on?

MS. WALES: Yes, put into irrigation water then spray it out over the field. When it's applied by

chemigation, after the treatment, a -- enough clear water is ran afterwards through the sprinklers to produce a one-inch seal of water, and also to drive the Metam-Sodium into the soil.

When it's injected by soil-injection methods, use special equipment that injects it about 10 to 12 inches into the soil. Afterward, the soil is bedded or tarped or rolled and compressed. The purpose of this is to keep the Metam-Sodium -- actually, the MITC vapors in the soil so they actually do the fumigant activity.

The conversion in the soil of Metam-Sodium to MITC occurs within about an hour. And conversion occurs with 87 to 95 percent efficiency, depending on some conditions of soil. Increased soil temperature, increased concentrations of clay or organic materials, and increased soil pH, coupled with decreased soil moisture content, lead to rapid -- more rapid conversion.

Two other compounds may be formed in the soil during that conversion. One is carbon disulfide and the other is hydrogen sulfide. The generation of those compounds really depends on the pH of the soil. If it's more alkaline, hydrogen sulfide is expected to be generated. And in basic soils, carbon disulfide.

About 60 percent of the MITC that's generated in the soil volatilizes, leaves the soil and

enters the air. Once in the air, the main pathway for the loss of MITC from the air is through photolysis. The photo decomposition results in a variety of compounds, as you can see on this overhead here.

MITC is there on the left. The activated molecule is the one in the middle with the star. And according to Geddes, the major, primary photochemicals produced is methyl isocyanide. About 80 percent of the MITC is converted to methyl isocyanide.

That follows some secondary photochemical processes and results in methyl isocyanate, and methylformamide, and some other compounds which you see here. Geddes proposed that the -- the methyl isocyanate may be the -- may be photochemically stable, because he observed that it increased over time.

Next page. Briefly to cover the use of Metam-Sodium --

DR. BLANC: Can you go back to the last slide?

MS. WALES: Sure.

DR. BLANC: Point out to us which formulas -- which moiety --

MS. WALES: I'm sorry. I can't hear you.

DR. BLANC: Which chemical structure is which?

MS. WALES: If you follow the main pathway, that's MITC.

DR. BLANC: Yeah.

MS. WALES: That's MITC, the activated state. To the right of that is methyl isocyanide. To the right of that is methyl isocyanate. A-ha. This structure right here is N-methylformamide. This right here is methylamine. Methylamine is also generated in this pathway. This is carbonyl sulfide, sulfur dioxide, and in this pathway, you also generate the MIC plus hydrogen sulfide.

DR. BLANC: Thank you.

MS. WALES: This is -- this slide shows overall Metam-Sodium use in California. This is, once again, in the agricultural setting, from 1990 through 1998. As you can see, Metam-Sodium use began to increase in 1994. It is pretty-well stabilized at about 15 to 16 million pounds a year since then.

The reason for this increase in 1994 was largely due to two things. One was the reduced use of telone, 1-3 dichloropropene, which is another fumigant, and methyl bromide. Also, researchers discovered that Metam-Sodium was very effective in controlling root nematodes in carrots, and also nightshades in the nightshade crops. So they applied -- so use went up to

account for that.

Next slide. This is the use of Metam-Sodium from 1990 to 1998 on a month-by-month basis. You can see that it's used pretty much year round. However, there are couple large peaks. The first one, right here in February through April. And another peak that occurs in the late summer, early fall, from about July through October. And this is throughout the whole state.

As I said, Metam-Sodium is primarily used on carrots. Almost 30 percent of what's applied in California is used on carrot crops. Another 25 percent -- 23 percent is used on tomatoes, cotton, and potatoes account for the major crops. All the rest of the uses are from a variety of crops -- root crops, bulb crops, lots of different crops.

When we say that the use is associated with a crop, it's actually a pre-plant application. It's applied before the crop is put in the ground. This map shows how Metam-Sodium is used throughout the state. This is from 1998 --

CHAIRMAN FROINES: Question.

MS. WALES: Uh-huh.

CHAIRMAN FROINES: This document that we had earlier this morning, Monitoring Multiple Chemicals by Crop Root, and he's got the 23 chemicals for cotton.

MS. WALES: Uh-huh.

CHAIRMAN FROINES: And Metam-Sodium is not listed on this list. So there's a disconnect between your 11 percent here, and this document. Which seems -- would seem to imply that -- well, they're different. Anybody know the answer to that?

MR. SEGAWA: I do.

CHAIRMAN FROINES: Oh, there you are. I keep looking for you.

MR. SEGAWA: That's because, in the chemical listed for cotton, I only listed those chemicals which had their highest use on cotton. And in this particular case, you can see that highest use is on carrots. And so in the crop grouping, it would have been grouped with carrots, rather than cotton.

CHAIRMAN FROINES: Okay. For us, it's probably better to know which is the highest pesticides on cotton.

MR. SEGAWA: Yes. For instance, we could have one -- I just put the highest crop use. I could have put highest two or highest three crops, which would have been another way to do it.

CHAIRMAN FROINES: Well --

DR. GLANTZ: Well, no. I think the difference -- I think what you're saying, John, is the

list should have been a list of the -- of the pesticides used on cotton, perhaps. And what he did was, he said, let's look -- it was the other way around.

It said, let's look at the pesticides and pick the crop that each pesticide is used the most on. And those are the -- the ones on the list we had earlier were the pesticides where cotton was the most heavily -- was the greatest use of that pesticide.

CHAIRMAN FROINES: But you see the potential contradiction?

DR. GLANTZ: Yeah, yeah. I just think you need to be clear, though.

CHAIRMAN FROINES: So we -- so the panel, you see, doesn't know right now what are the most important pesticides on cotton.

DR. BLANC: Because -- to follow up on that, you could have a pesticide which actually isn't used that much anywhere, but the one crop that it is used on is cotton; right?

MR. SEGAWA: Correct.

DR. BLANC: And another pesticide which is used, like Metam-Sodium is -- only ten percent of it's used on cotton, but it happens to be one of the most widely used pesticides in California. Therefore ten percent of 13 million pounds is still a million pounds

used on cotton.

MR. SEGAWA: That's correct.

DR. BLANC: And so, therefore, what would probably interest us more would be, of the heaviest-use pesticides overall in California, which are -- which of them are used in rank order in cotton? So that if you talked about one crop --

MR. SEGAWA: Yes, but then we would have to come up with some sort of cut off. As you say, one million pounds -- everything above one million pounds, we have concerns about. Everything below, we do not monitor for.

DR. GLANTZ: Or some reasonable cut off. Just show us -- or show us if you use a cut off of one million pounds, then you use it to cut off 500 thousand pounds. How does it change?

CHAIRMAN FROINES: I mean, we're interested in the scope of the problem. And so, if you arbitrarily limit that, we're left without a real sense of what -- what's the pattern of use, basically. Let's go on.

MS. WALES: Next slide. Map of the 1998 use in California. This is of Metam-Sodium. So you can see the bulk of the Metam-Sodium is applied, once again, through the Central Valley. Heaviest -- these darkest spots are the highest use.

The highest use is in Kern County. This is 1998 now. We have Kern County, and then up through Fresno, that's quite a bit in Madera area. And then on down here in Imperial County. But you can see, it's also -- it's used pretty much through all the agricultural areas. Including, if you look up at the north part of the map there, you'll see some use on the potatoes up in Modoc and bulbs, I believe, in Del Norte.

Now, these things that I've mentioned about the locations of where it's used and also the soil conditions actually played a big part in determining where we wanted to do our studies. The ambient studies were designed to measure pesticide concentrations in ambient air during the time and region of peak use.

The samplers were placed on roof tops of schools, fire houses, and other public buildings. And for ambient studying -- studies, we did not associate the monitoring with any specific application. This was to provide an estimate of exposures that people living in proximity to pesticide applications might experience.

Three studies were conducted in California, and they're summarized in the report. This is a table with the information from the three studies. I'm not going to read this to you in the interest of time. And especially since Tom, who's after me, is going to cover a

lot more of this in exposure assessment.

What I did want to point out to you, was that the ambient studies were conducted in Kern County, and in Lompoc, and then again, very new study that was just published this year in Kern County. And these were conducted in the summertime.

Dr. Seiber's study went from May until August, and then the Air Board study was in July. And in Kern County, we have soils in the summertime that are very warm. They're dry. The pH is a little bit on the alkaline side. And the soil-moisture content is low. And so that would indicate that that's probably the best time to find MITC in the air.

These are the positive-sample results. And the number of samples that were taken and then the number of samples -- of the positive samples. This recent study by Dr. Seiber did something a little different than the others did. And that was, he put monitors inside residential homes, outside residences, very close to the external walls of the homes.

And then he also placed monitors on tops of roof tops, other public buildings in the Kern County area where Metam-Sodium was being applied. Interesting thing to notice is that the positive detections indoors was not that much different from the outdoors, and the ambient

studies or ambient samples.

In the wintertime, he took samples in January and in March. And now, those cool air/cool soil conditions, and the results are much lower than what they were in the summer studies. This is a map from the study that was conducted by the Air Board of 1993. Hard to see, because it's not on the scale here.

But the samplers were placed in Shafter and Bakersfield, in Lamont, and Weed Patch. The red hashed marks and checker-board marks that you see here on the map are where the applications of Metam-Sodium occurred during this study.

As you can see, we had applications surrounding all of the areas. An interesting thing that I noted was that at Bakersfield, which was the background site, there were positive detections in all eight of the samples that were collected. And the nearest applications of Metam-Sodium were approximately six miles to the northeast -- or to the northwest, and about seven or eight miles to the southeast.

CHAIRMAN FROINES: On your previous overhead --

MS. WALES: Uh-huh.

CHAIRMAN FROINES: -- you say "ambient air monitoring, MITC." My guess is that you mean

Metam-Sodium.

MS. WALES: We're monitoring for MITC after applications of Metam-Sodium. Because Metam-Sodium is not volatile, we don't expect to find it in the air. Also, because conversion is so rapid, yes.

CHAIRMAN FROINES: But it's a Metam-Sodium application.

MS. WALES: It's a Metam-Sodium application. One other thing to note, I checked. There was no Dazomet or MITC applied anywhere in Kern County during the course of the study. So all of the results would presumably be from the Metam-Sodium applications.

This is from the Lompoc study. Now, while this study wasn't conducted solely for Metam-Sodium, one of the chemicals was Metam-Sodium. There were -- samplers were placed at these locations around the city of Lompoc. And two applications were made during the study, one right here, and the other one is right here.

DR. FUCALORO: Just one question. Came up when I was reading the report. A -- AI, what does that stand --

MS. WALES: Active ingredient.

DR. FUCALORO: Thanks.

MS. WALES: Okay. On the application site air monitoring studies --

DR. GLANTZ: Before you go on, on this figure 11-A, I'm a little confused.

MS. WALES: The Lompoc map; okay.

DR. GLANTZ: Yeah. Where -- were the -- is this whole gray area where it was applied? That's the city of Lompoc; right?

MS. WALES: Yeah. Let's go back to that map.

DR. GLANTZ: So where is the actual -- is the actual application a little box sort of on the --

MS. WALES: Yeah, on the map here, it's purple. This is the city of Lompoc. This is where one application occurred.

DR. GLANTZ: I see.

MS. WALES: That was the 1,058 pounds were applied. And then this field right here to the -- almost due west --

DR. GLANTZ: I see. Okay.

MS. WALES: -- is the 952. For the application site monitoring studies, we have five studies that were conducted, and they're summarized in the report. Once again, I'm not going to -- on the next slide I have a table. I'm not going to read all this again.

However, two of the studies were from -- were based on sprinkler irrigations. One of them we

monitored for MITC, hydrogen sulfide, and carbon disulfide following a sprinkler irrigation application. And then these are the results.

Tom is going to discuss this a lot more following me, so I'm not going to say much, other than we did detect hydrogen sulfide. And that could be expected because of the alkaline of the soil. And we did not detect carbon disulfide.

Three studies were done following soil injection. One in 1993, one in 19 -- all three -- well, two in 1993, and one in 1995. And once again, following the application, MITC was detected in all of the samples -- nearly all of the samples in all of those studies. There are no questions? Tom.

CHAIRMAN FROINES: Thank you.

MS. WALES: Thank you.

DR. BLANC: Actually, I have one question. Sorry.

MS. WALES: Oh, okay.

DR. BLANC: Because this may not be covered later.

MS. WALES: Okay.

DR. BLANC: Your third overhead --

MS. WALES: The third one?

DR. BLANC: -- where you talked about the

structure of Metam-Sodium and Dazomet.

MS. WALES: Okay.

DR. BLANC: So is the -- should I assume that each molecule of Dazomet yields two molecules of MITC as opposed to Metam-Sodium on the one-for-one basis?

MS. WALES: According to the manufacturer of the one -- of one of the Dazomet products, when Dazomet breaks down, there's a ring --

DR. BLANC: Rearrangement?

MS. WALES: Well, a ring break that occurs. And you yield one molecule of MITC, one molecule of formaldehyde, one molecule of hydrogen sulfide, and one molecule of methylamine, I believe. And together, that whole collection of compounds constitutes the active.

DR. FUCALORO: In the presence of water; right?

MS. WALES: In the presence of water, yes.

DR. BLANC: Say it again. One molecule of MITC, one molecule of formaldehyde --

MS. WALES: Of formaldehyde, one molecule of hydrogen sulfide, and one molecule of methylamine, I believe. Let me check to make sure. Yes. Formaldehyde, MITC, hydrogen sulfide, and mono-methylamine.

CHAIRMAN FROINES: What is it again?

MS. WALES: I'm sorry?

CHAIRMAN FROINES: Say it again. Methylamine --

MS. WALES: MITC, formaldehyde, hydrogen sulfide and mono methylamine.

DR. BLANC: What's the form of formaldehyde?

CHAIRMAN FROINES: CH2O. There are two formaldehydes.

MS. WALES: You would get two?

CHAIRMAN FROINES: You said methylamine, MITC, H2S and formaldehyde.

MS. WALES: Yes.

CHAIRMAN FROINES: Seems to me you get two formaldehydes. What am I missing here?

DR. BLANC: You got to get something different, because there's five carbons in this molecule.

CHAIRMAN FROINES: You get MITC, H2S, methylamine --

MS. WALES: And formaldehyde.

CHAIRMAN FROINES: So you have to have two formaldehydes.

MS. WALES: That could be.

CHAIRMAN FROINES: Break the bond between the -- you look at the sulfur. You break the bond between the two sulfur breaks, break the bond between the hydrogen, the methylamine, you can see you take that right

out. See, the MITC is the right-hand side, so you've got two carbons unaccounted for. So that must mean two formaldehyde.

MS. WALES: That could be.

CHAIRMAN FROINES: I'm sorry. Thank you.

MS. WALES: Is that good? Thank you.

DR. THONGSINTHUSAK: My name is Thomas Thongsinthusak. I'm with DPR. My presentation will come -- will cover part B, the exposure assessment of the MITC. Next one, please. My presentation will cover six different topics, starting from estimate production of MITC in California and the calculated exposures for adults and children. And so I touch on the production of MIT, hydrogen sulfide, and then exposure appraisal.

Next please. Estimated production of MITC in California. I use the -- use report format and sodium from 1992 to 1997 and the amount of Metam-Sodium, MITC are shown as million pounds. The first column, Metam-Sodium use in California in 1992, is about 8.6 million pounds. And the amount was doubled in about 1995.

This is the column show the MITC generated from Metam-Sodium use. This column here. I use the equation shown in foldout B. The conversion of Metam-Sodium to MITC is about 60 percent by weight, which is about one mole of Metam-Sodium per one mole of MITC.

The amount of MITC products used in California is very low. For 1992, it's about 8,500 pounds. In 1997, it's about 400 pounds, only.

In the last column show the total estimate amount of MITC produced from '92 to '97. The last part of this slide show the amount of use of the estimate in California. Which is -- California, which is very small compared to amount use of Metam-Sodium.

Next slide, please. This slide show the calculation of the exposure estimates calculated for adults and children. The -- first of all, I use the data from what Pam mentioned, and then those of amount of concentration of MITC were adjusted for molecular weight, and application weights, and a percent recovery.

First of all, I use the MITC concentration times the maximum application rate, divided by the application rate, if known or used in the study, and then divided by percent of self-recovery. I can convert from the amount expressed as microgram per cubic meter to parts per billion using this equation.

The estimate calculated as an observed daily dosage or ADD. For ADD I use the short-term concentration of MITC times adult female ventilation rate and divided by body weight. Short-term ADD concentration, that means 24 hour times average or closest to 24 hour TWA. Further

exposure estimates for male -- adult males, I can use the factor of 1.5, which is obtained from the ratio of ventilation rate and body weight between males and females.

The next is the long-term or moderate-term exposure estimates for MITC or seasonal average daily dosage or SADD. The ADD that used to calculate the SADD is used from the moderate term, ADD concentration of MITC times exposure days per season 120-days season. For the exposure days, I used 23 days per season. Currently DPS is working on exposure days for current exposure assessment.

This slide show the ADD for adult females. And for B.2, B.7, and B.8, they were from ambient monitoring studies. And the first one, wherever I can, I will use the Atkinson concentration as TWA. And if they were not available, I will use the highest exposure -- highest MITC air concentrations.

In this case, only one applicant from each site. I use the highest concentration. This study was conducted in --

DR. GLANTZ: What was TWA again?

DR. THONGSINTHUSAK: Times weight of average. This study was conducted in 1993. B.7 conducts in 1997 and '98. As it's shown earlier, the amount of use

of Metam-Sodium for B.7 in California was about doubled to the amount of Metam-Sodium use in 1993. The range of the ADD from .62 to about 5 for B.2, B.7. They were very similar to B.2. For the study in Lompoc, the ADD was about .14 micrograms per kilogram per day.

Next slide, please. This table show the ADD obtained from five studies. This is application site studies. Contra Costa, B.3, and Kern County. And B.4 also in the Kern County. B.5, Madera. And B.6, Bakersfield. There will be one more study that will be added in the future. The industry conducted one latest study. I will add that study, once the final report is available.

There's a wide range of ADD from application site study. When I say it doesn't say how far away from the treated field, it's normally range from 12 to 40 yards from the treated field, kilometers. You can see that the farther away from the treated field, pyramid of the ADD is lower than the station that is located closer, like five meters. Next, please.

CHAIRMAN FROINES: Will you then use these now for the MOE calculations?

DR. THONGSINTHUSAK: Next person, Andy Rubin, will use these ADD for MOE calculations.

DR. BLANC: Why do the ranges on these ones

that you have here differ from the ranges on the last slide that Pam showed us?

DR. THONGSINTHUSAK: That Pam show?

DR. BLANC: Yeah, for the same studies. For example, for the Madera County, she had a maximum -- a range of 1.29 to maximum of 435 parts per billion. And you have a series of ranges, but none of them are as high as 435 parts per billion. Whereas, your Kern County one there, range -- upper range is higher than the upper range.

DR. THONGSINTHUSAK: Pam's data have not been corrected for the maximum application weights and the percentage of recoveries. In my case, before I calculate the ADD, I will make adjustment for maximum application weight, and the percentage of recoveries.

DR. BLANC: So your value will always have a slightly higher --

DR. THONGSINTHUSAK: Pardon me?

DR. BLANC: So your values will have a slightly higher upper range?

DR. THONGSINTHUSAK: Yes, in most case, they will be higher. Next is to calculate the seasonal average daily dosage. I will use the ADD concentration from a moderate-term air monitoring studies. In this case, I will have more samples like for B.2.

For B.2, B.7, and B.8, represent ambient air monitoring data. And I calculate use ADD, multiplies exposure days per 120-day season. And the range is like for the B.2 from .02 to about .45. I will not go over all these numbers. They are in your handouts.

Next, please. The SADD from the application site monitoring studies, five studies all together. And for the first one, B.1, 27.2 micrograms per kilogram and per day. And the numbers vary according to the sampling site, based on the distance from the treated field kilometer.

Next, please. Now, there's a question about a potential retention of MITC on silica gel drying tubes which is placed in front of a charcoal sampling tubes, not only in a sampling tray. There will be section of the tubes, the front will be the silica gel drying tube, and the other two absorb the excess moisture, and the other two will be the charcoal sampling tube.

Normally, there will be two sections. The first section will contain 400 milligrams of charcoal, and subdivided by -- and the last part will contain about 200 milligrams charcoal.

Most studies use just charcoal tubes to collect their samples. But there are two studies that use the silica gel drying tubes. The first one by Wofford in

1994, and the second one by Zeneca -- okay. They found right by -- Wofford found at four out of ten tubes of the silica gel, they can retain from zero to four percent of the total MITC. And for the internal two, the retention ranged from 58 to a hundred percent. So there's a question there.

Silica gel may retain some MITC, but it is -- doesn't seem to be so from the study by the industry. The recovery of MITC range from 71 to 95 percent. So in this case, after desorption deficiency correction, retention would be -- should be around ten percent or less. Next, please.

DR. BLANC: Can you say what the implications of this is?

DR. THONGSINTHUSAK: Pardon me?

DR. BLANC: And what do you believe the implications of these data are?

DR. THONGSINTHUSAK: The implications? The implications of those data is, it's likely that silica gel drying tubes can retain some MITC. But I have got to have some more proof for that. And most studies accept the tube. Most study does not use silica gel drying tubes. So, in general, I do not see any problem for that.

DR. BLANC: But you said that Wofford used silica drying tubes.

DR. THONGSINTHUSAK: Yes.

DR. BLANC: And the highest values that you had were from the Wofford study.

DR. THONGSINTHUSAK: Yes.

DR. BLANC: And if the retention was high, means that you couldn't remove some of the material, and therefore underestimated those very high values; is that right? Did I have the direction of the effect?

DR. THONGSINTHUSAK: Yes. If the Wofford study did not include MITC in the silica gel tubes, but they did. So they combine MITC from both -- both types of tubes. So there's no problem for that. But that's another study conducted by Zenneca. They did not analyze MITC in the silica gel drying tube. But from the lab from the study, they did not see that that is an important issue.

DR. BLANC: And did you use their data in any of your calculations?

DR. THONGSINTHUSAK: Yes, uh-huh.

DR. BLANC: Which calculations involved the Zenneca study?

DR. THONGSINTHUSAK: I think B.6.

DR. BLANC: B.6? The Bakersfield study?

DR. THONGSINTHUSAK: Madera, I think. Madera. Would you show the table 7.2?

DR. BLANC: 7.2 or 8.2?

DR. THONGSINTHUSAK: B.5. Madera. Actually, it's ICI. They used silica gel drying tubes, but they did not analyze MITC in the tube.

CHAIRMAN FROINES: They didn't analyze the MITC in the --

DR. THONGSINTHUSAK: Silica gel.

CHAIRMAN FROINES: So that underestimates the overall approach.

DR. THONGSINTHUSAK: It is possible that MITC concentrations were underestimate. But as I mentioned before, from their study, the recovery with or without silica -- with a silica gel drying tube was very high. So I assume that it is not their concern, because of the their findings.

CHAIRMAN FROINES: Well, it seems to me, this is actually an issue that needs to be resolved. It's not enough to say, "I think it was not important." That's -- that's -- I think falls in the category of a subjective comment. I think the issue is, is it important on a quantitative basis?

DR. THONGSINTHUSAK: I agree. Thank you.

CHAIRMAN FROINES: So the point is, if we're going to be using silica tubes to remove water, then we need to know, one, is there a material being absorbed, and

two, can you -- what's the efficiency of desorption to determine the residual?

DR. ATKINSON: It should only effect the ICI, whether it's analyzed the silica gel.

DR. THONGSINTHUSAK: The reason I cannot make an adjustment for this set of data, because I don't have any solid information to make an adjustment. Because from the study by Wofford and her colleagues, it show a high and low. And normally, the temperature or the relative humidity will affect that.

But from the two intervals, the relative humidity and the temperature are very similar. So I don't know what cause that -- what cause the absorption or absorption by silica gel. Okay.

CHAIRMAN FROINES: I state -- I only press it insofar as goes back to the same old, same old, same old, which is, if we're using MOEs to determine toxic air contaminants, then these kind of matters become part of the uncertainty and the exposure characterization. They therefore become elements in the actual designation of the compounds of TAC. So it actually becomes potentially significant, in a broad policy context.

DR. FUCALORO: It's kind of worse than that. When you talk about uncertainty, you're talking about quantitative thinking. And this is just uncertainty

in knowing what the meaning of the number is. Can you put it -- from what you know, can you put an uncertainty in some of these numbers?

DR. ATKINSON: Must be able to.

DR. FUCALORO: And then just get --

DR. ATKINSON: If the recovery is between 75 and 95 percent you can bracket --

DR. FUCALORO: You can bracket, it seems.

DR. THONGSINTHUSAK: Can you put table 7.2 back again? I would like to point out one more thing. Lynn Baker pointed out to me, actually. Under Wofford's study, I can say that this is the worst case here, because the -- they use the silica gel drying tube. And you compare -- this stands from the five meter to air concentration up to 1100. But the same distance under ICI, a hundred and eighty-six.

This seem to represent the worst case. They were -- when we compare the same distance from the field parameters. 450, and from Wofford's study, 468. Similar distance from ICI, a hundred and eighteen. So I assume that for the first -- before represents the worst-case air concentration of MITC. This one compared to this one. May I move on?

CHAIRMAN FROINES: I'm confused, but maybe we'll deal with it later. Did you understand?

DR. BYUS: Which number are you going to use to calculate the MOE?

DR. THONGSINTHUSAK: Both. Both.

DR. BYUS: You're going to use the low one and the high one?

DR. THONGSINTHUSAK: Yes.

DR. BYUS: Why? Just out of curiosity.

DR. THONGSINTHUSAK: We will show the worst-case MOE, as well as the MOE for the lower air concentrations.

DR. BYUS: But the lower one could very well be due to an analytical error and not getting total recovery. So I mean, in a sense, what Dr. Froines' been saying, yes, you could put a value of uncertainty on that number based upon your clear understanding of the analytical difficulties.

So I would -- I mean, we'll get to this. But off the top of my head, I would tend to go with the higher values for the MOE, and not even bother calculating the lower ones, since you know that there's an analytical error, perhaps, in the generation of that number.

DR. THONGSINTHUSAK: Yes, we can disregard this study, because of the deficiencies.

DR. ATKINSON: Well, the ICI ones could be increased by about 50 percent, since they are the recovery

70 percent, apparently.

DR. THONGSINTHUSAK: But if it's increased by a hundred percent, it's still less than half of the first one. That's the worst case.

DR. BYUS: My understanding, that's kind of Wofford's estimation of analytical problem, not actually --

DR. ATKINSON: That was ICI.

DR. BYUS: Was it ICI's numbers? I just don't --

DR. ATKINSON: That's what I got out of it.

DR. BYUS: Okay.

CHAIRMAN FROINES: Let's go ahead. Let's go ahead. Are you throwing your hands up or do you have a comment?

DR. BLANC: I was wrestling paper.

DR. THONGSINTHUSAK: I also estimate the exposure of children to MITC. I used the data calculated for adult females times a correction factor. And this correction factor is 4. And correction factor was calculated from ventilation rate of children and body weight of children versus ventilation rate and body weight of adult females.

CHAIRMAN FROINES: Can I go back and ask you a question?

DR. THONGSINTHUSAK: Yes.

CHAIRMAN FROINES: When -- when these determinations are made, whether it be ICI or Wofford or Caar, do you have written down somewhere what the meteorology is? Do we know where you're upwind and downwind of the application? I mean, the numbers can vary widely depending upon --

DR. THONGSINTHUSAK: Yes, in my document, I mentioned that most short-term and long-term, moderate-term air concentrations were from downwind MITC concentrations.

CHAIRMAN FROINES: They were downwind?

DR. THONGSINTHUSAK: Yes.

CHAIRMAN FROINES: Do you have the characteristics of the meteorology?

DR. THONGSINTHUSAK: There's some data in the report. And then I picked the MITC according to the downwind direction. So that would be a wind direction of different directions. I picked downwind and picked the air concentration according to the downwind direction. Except two. I forgot which one. That they were not in the downwind direction. I mentioned that in the document, which one.

DR. FUCALORO: So you have some description, although it's not necessarily very detailed?

DR. THONGSINTHUSAK: Yes, that's right. So whenever I can, I will use a downwind air concentrations of MITC.

CHAIRMAN FROINES: And presumably you've calculated the distribution of your data, as well as these means. Because it seems to me that one doesn't want to use the mean for an MOE calculation.

DR. THONGSINTHUSAK: I presented both mean and the range. The range -- the ranges are in the parentheses. So there were too many, so I did not go over those ranges. May I proceed?

CHAIRMAN FROINES: Yeah, please. I'm sorry. I think this issue of distribution is one that we want to talk about.

DR. THONGSINTHUSAK: Okay. There was some concern about a production of MIC, CS2 and H2S, hydrogen sulfide. There were two studies that found MIC and CS2 and H2S, the first one by Air Resources Board, for MIC from the downwind direction, the range of .4 to 2.5 parts per billion. For the overall MIC production of recover from range from .3 to 2.5 parts per billion.

This the only study that analyze MIC, as far as I know. For carbon disulfide, 8 out of 16 samples detected under the detection limit of 4 parts per billion. For hydrogen sulfide, there are three ranges.

The first one is from 3 parts per billion to 76 parts per billion. This is the sampling from one to four hours. From five to seven hours, non-detectable, and from 21 to 24 hours, non-detectable up to 8 parts per billion.

Next, please. My final slide shows my exposure appraisal. For the number of exposure days that were used to calculate the SADD were obtained from limited surveys and other information. We use currently 23 days. But the industry suggested 8 days per season.

I mention number two about silica gel drying tube can retain MITC in two of the studies. The study by Wofford combine MITC recovered in silica gel tubes, plus MITC recovered in charcoal sampling tube.

Currently there's a technical information relating, which is the guidelines for all application methods for Metam-Sodium in California. This is the guideline issue by the industry. And that's the way to reduce the emission of MITC from sodium.

Many studies conducted in the past were not in compliance with these technical information relating. But the exposure, especially those that sampled inside are shorter than the buffer zone, maybe overestimate the exposure for residences by standards.

DR. GLANTZ: Well now, is that -- is that because of something unusual about this exposure or about

these applications? Because it would seem to me, just as a person who occasionally has used pesticides, that I don't always exactly follow the exposures, you know, because I'm a clod or something.

And so, I mean, is there any evidence that the -- that the exposures that you were monitoring are in any way unusual? Because, if they're not, and given that people sometimes don't follow the guidelines -- probably a lot of times don't follow them, would seem to me, this last conclusion is unwarranted.

DR. THONGSINTHUSAK: Yeah, that's possible. And we still don't know the compliance rate, even though this technical information bulletin is attached to product labels.

DR. GLANTZ: Right. Right. Well, given that, I mean, if you have actual data in the field, I would believe that over -- rather than saying, well, we're just going to assume that we had a few odd people who didn't follow the technical specifications the manufacturer produced.

DR. THONGSINTHUSAK: That is very likely to happen.

DR. GLANTZ: Yeah. Well then, that's why I would say the last statement you have here about overestimating actual exposure, you don't have any

evidence to support that statement.

DR. THONGSINTHUSAK: Sorry. Go ahead.

DR. BLANC: Go ahead.

DR. THONGSINTHUSAK: If you think that's not appropriate, I would remove that. I agree to do that.

CHAIRMAN FROINES: We're going to take up the whole document. So probably don't need to -- should avoid -- we should take up major issues and avoid --

DR. BLANC: Well, isn't a major issue the fact that if the application amount has doubled in the time since the sampling was done to the present, there needs to be some comment in the document on whether or not the use patterns in terms of doubling is because of added acreage that's used versus added pounds per acre when it's applied.

And also whether or not the sampling that was done representing certain isolated fields being sampled -- being -- having use is really applicable to the real-world use where there might be much bigger areas used simultaneously.

I don't know the acreage of these little plots where the application was. But if the application has doubled -- if it's doubled in a geographic area -- if that's consistent across geographic areas, and not simply that there are new geographic areas that have been

recruited, then the actual exposure areas would likely be twice as high.

DR. THONGSINTHUSAK: I can double check on the area, if it correspond to the amount of use.

DR. BLANC: But you know what I mean?

DR. THONGSINTHUSAK: Yes.

DR. BLANC: If within a three-square-mile area of Lompoc five years ago over a two-week period there would be, you know, 50 acres where it was applied over that time period, and now it's a hundred acres, then the exposure would probably be higher or the -- you know, I mean, the sampling is very dependent on how many acres -- over how many acres applications occurring at the time that you're sampling.

CHAIRMAN FROINES: Stan, what time is your plane?

DR. GLANTZ: Quarter -- I have to leave about a quarter to 2:00.

CHAIRMAN FROINES: If we go to 12:30, break for lunch, that's 1:30. Have 45-minute lunch, that's 1:15. We get about a half hour on MTBE with you. Let's go ahead and we're going to try to bring this discussion to closure. May be tight, but we're going to try to bring this to closure by 12:30. I really want Stan to have input on MTBE.

DR. GLANTZ: Actually, I was going to suggest, because I am a little worried about that. Maybe we could table -- finish this one part of the presentation, and maybe do MTBE, and then come back to this. Because I'm a little worried about having to leave in the middle of that discussion.

CHAIRMAN FROINES: Okay. You want to break to lunch and then come straight back to MTBE and then take this up?

DR. GLANTZ: Yeah. Or work through lunch, if people want to do that.

CHAIRMAN FROINES: Is that okay, Paul? Or who's ever handling this presentation? I'm very worried about not getting to MTBE with Stan gone. Can -- can we defer till after lunch, after the MTBE discussion?

MR. HELLICKER: Sure. We're here at your disposal today. We do have another segment to this presentation.

CHAIRMAN FROINES: Yeah. I think -- I hate to hurry that, because we're all the health types, and so we're interested in hearing that part. So -- but I know we're -- what's going to happen. Things -- time drifts a little bit more than -- even if I thought we could be done by 12:30, you know. It's -- so let's take a 45-minute break for lunch. Then let's do MTBE. Then we'll go

straight back to MITC.

(Lunch recess taken.)

CHAIRMAN FROINES: We'll take up MTBE. And I want to quote two sections from the transmittal letter from Michael Kenny to me. He said,

> "This letter is to formally request the Scientific Review Panel review the Office of Environmental Health Hazard Assessments' enclosed documentation on the carcinogenic potency of methyl tertiary butyl ether in accordance with the usual procedures for peer review of the health values for toxic air contaminants."

So that's the defining question. Now, say more about that in a second. Secondly in his letter, he says the following:

> "On April 26th, 1999, the Air Resources Board requested OEHHA to develop health values for the air exposure pathway for MTBE. OEHHA's assessments incorporated carcinogenicity information already contained in the technical support document compiled for the public health goal for MTBE in drinking water and the recent report on MTBE completed by the University of California."

Because of that request, it means that this

panel is now going to, in part, be reviewing the public health goal. But this letter also includes the recent report completed by the University of California, which I was responsible for the health-effect section.

So what I have decided to do, to avoid any appearance of conflict, I don't want to be in the position of defending my document. And so what I decided to do was to transfer the chair for this discussion to Tony Fucaloro, who will chair the discussion.

But I also felt that I had no reason to not be able to participate in the discussion as a scientist who's familiar with MTBE. So Tony is going to take it over.

Last thing I'll say is, came up last time, we are basically voting on the following: We are voting to determine that the health effects report is based on sound scientific knowledge, methods, and practices. "Scientific Review Panel determines that the health effects are based upon sound scientific knowledge -- sound scientific knowledge, methods or practices," that criteria.

DR. BLANC: Tony, I'd like the record to show that there is consensus on the panel that John's approach to handling this matter meets with our agreement.

DR. FUCALORO: Sure. I think if I -- if I

look around -- ask around the table, I see no problem. I personally would have had no problem with John chairing this section. But I also have no problem -- I have a little problem with my chairing. Means I have to work harder. But other than that, I have no problem with it. And does anyone disagree with what I just said? Speak now. So --

DR. GLANTZ: Is this why -- never mind.

DR. FUCALORO: I think that certainly approved by the panel to follow John's suggestion on this. To refresh your memory -- and I've had my memory refreshed on this -- MTBE, methyl tertiary butyl ether, is a TAC by virtue of being an HAP. It's a toxic air contaminant by virtue of being hazardous air pollutant designate by the U.S. Government.

So -- so it is a TAC. So what is our purpose here? Our purpose is to validate a document prepared by OEHHA, actually applying some risk factors -- stating some -- some risk factors that they've estimated so that MTBE especially -- I mean, important especially because of the clean up one anticipates for MTBE in the groundwater and vapors that would come from that groundwater. With that in mind, is there a presentation from OEHHA at this point?

DR. MARTY: No, we actually gave the

presentation at the last meeting, so we don't have --

DR. FUCALORO: I do recall. And the document that you are handing out to everyone is a document that was handed out at the last meeting. And this is the document which we are to find as being based upon sound, scientific principles; is that correct as you understand is it?

DR. MARTY: We sent that document out, along with the public-health-goal description to the panel members, and I'm recalling the middle of September.

CHAIRMAN FROINES: This document?

DR. SALMON: Yes.

DR. MARTY: Yes.

DR. FUCALORO: And -- and Attachment 1 is essentially a condensation of that document in terms of the -- at least the part that you're interested in, the potency factors.

DR. MARTY: It's a condensation, and also the presentation of how we derived unit risk factors for inhalation exposure.

DR. FUCALORO: Now, we discussed this. And I'm going to call upon the panel members to make comments about it. So I want to give you -- want to give you a head's up on that. But I will -- I will indicate that I recall some of this -- I recall a lot of this

conversation, now that I've seen the document. And one of the concerns was that these numbers were based upon studies that use very high concentrations of MTBE.

And there was some concern by some members on this panel that -- that we were looking at problems associated with clearing of the chemical in the mice or rats -- that is, mice studies. And I think that was at issue. Is that your recollection?

DR. MARTY: I'm recalling that people were concerned about the carcinogenistic bioacids using high doses. However, that is not unique to MTBE.

DR. FUCALORO: I'm not asking to you defend it. That was the issue.

DR. MARTY: That was one issue that was raised.

DR. FUCALORO: So with that, I would ask if there's anyone wants to add to it, because we're going to have to vote on this, it seems to me.

DR. GLANTZ: Well, I -- since I have sort of limited time here -- why are you smiling? The --

DR. FUCALORO: She's grimacing.

DR. GLANTZ: Okay. Good. Good. Well, my understanding of -- and this is a preface to a question. But I just want to make sure I understand what you did here. Is that you -- you took the oral data or the data

from drinking water, and you combined that with a pharmacokinetic model to get applied dose. And then you used the pharmacokinetic model on a couple of assumptions to figure out the equivalent inhaled dose to get the same target organs. And that's where the number -- the error number came from; is that correct?

DR. SALMON: The -- yes, the original studies on which the calculation is based -- in fact, the -- one of them is an inhalation study. But there's also an oral study. So what we were doing was using the pharmacokinetic models to enable us to compare all the data sets we had on a single basis.

And the pharmacokinetic model was actually used on the basis of the -- predicting the area under the curve for MTBE. That was the index parameter for the model. And the inhalation calculation for human exposure at low dose is related back to that metabolized-dose estimate.

So the pharmacokinetic model is basically used to tie together, on the one hand, the animal studies by either root. And on the other hand, the human exposure. Which for the PHG, actually, we used both an oral number and an inhalation number, because there's some, you know, secondary exposure by the inhalation root when you have drinking-water contamination. But in this

particular case for the TAC, we were interested specifically and only in the inhalation number.

DR. GLANTZ: Okay. Well -- so to me, everybody brings their own perspective to these things. The model and getting comfortable with the model is really the key part of this. And I had a couple of questions about the model. One of them -- and let me just tell you what they are. Just rattle through them, and then you can address them in whatever order makes the most sense.

So if you go to the drinking-water document -- I mean, I think from my perspective, and the things I know about, if I'm satisfied with the model, the -- to go from that to your unit risk for air exposure is just arithmetic. So -- and that all seemed reasonable.

But the questions I have is, if you look at table 10 of the drinking-water report, which is on page 72, you've got -- and this is sort of my standard question about these things. You've got a ton of parameters there. And, you know, how sensitive is the model to those assumed parameters?

How confident are you in the values of those parameters, if there are -- because it's -- a lot of this is just from one study or one or two studies, and then -- and then -- you know, if -- if these are off, how much difference does it make and what are the critical ones?

So that's one question I had.

The second question is, in here, you talk about using a polynomial model, but it wasn't ever quite clear to me exactly what that was or what the justification for using the specific model that you had was, you know.

Let me just ask all the questions, because I'm feeling kind of pressed for time. And I want to -- and you can -- and then the third question is -- and this may just be my own not understanding what you wrote here -- but if you look at tables 11 and 13, which is on page 73 and 75, which is presented as the -- as the validation of the model, and you guys say this stuff shows that the model works pretty well, as I read it.

And maybe I'm misunderstanding the table. It looked -- it didn't look like they worked all that well to me. So the -- especially at the high -- with the larger rats. And so what I'd like to you do is -- and then you can deal -- these are three interrelated questions -- is, I think it may just be my -- me not understanding these two tables.

But I need to be convinced, A, that the model parameters are reasonable, and that the model isn't overly sensitive to the values that you picked. B, why you used the polynomial model that you used, and what

effect -- how sensitive the results are to those assumptions.

And then C, to be convinced or explain how to read tables 11 and 13 to draw the conclusion that the model actually works pretty well. So that's what I'm looking for. You can put -- come back to them however is most efficient in terms of time.

DR. SALMON: Okay. Well, I'll start by talking about the parameters in the PBPK model simulation. By the way, the Borgoff Paper and the Row and Ginsberg Paper are actually describing previous modelling exercises which drew on quite a wide range of different data sources.

So in a sense, it's not just two papers that are the source of that. Those are in themselves compendiums and evaluations of the data which we choose to cite as prior authorities, basically. The parameters, all of which are essentially typical inputs for a PBPK model, are things like the compartment volumes and flows fairly generic sort of parameters which describe rats, basically.

And so those, to some extent, would represent sort of consensus values from the modelling literature. Neither we nor Borgoff would have -- you know, would have departed very far from the standard

assumed values for those.

The parameters which are a little bit more specific to the MTBE case are the partition coefficients and the metabolic constants. And certainly among the important issues are the actual values of the partition coefficients, which are usually estimated on the basis of experimental data. And we're using for this the precedents of the Borgoff paper.

And the metabolism, again, that is usually partly, at least, estimated from other experimental data. And that, in particular, can be an important one in determining how well the predictions of the model fit the observed excretion profile of the MTBE. This is where we transfer to tables 11, 12 and 13. Is that an adequate explanation?

DR. GLANTZ: Well, I understand that's where you got them from. But the concern that I have -- what I am interested in, is how sensitive are the results to the specific parameter values that you've got here? And of these large number of parameters, what are the important ones?

I mean, some of them aren't going -- I mean, we've been through this before with other modelling exercises. And some of the parameters aren't going to make much difference at all. And you can have big errors,

and it wouldn't matter. And other ones might be highly -- where the results might be highly sensitive.

And so, which ones are those, and how can you be sure that -- that, you know, that the risk numbers you're coming up with aren't highly dependent on parameter estimates, which may or may not be reliable?

DR. SALMON: Well, in terms of the model's sensitivity, I think probably the most critical parameters would be the V-max and KM values for MTBE. And the blood air and fat-blood partition coefficients. Those would probably be the most critical ones.

The -- as far as the extent to which we can validate our choice of the values which we're using there, for the purposes of this risk assessment, we are not using what I would call the details of the model. We're not trying to say, this is the concentration in the liver or the kidney or whatever.

So in a sense, our risk-assessment conclusion is not actually very sensitive to the finer details of the model. The only thing which we're actually using is the prediction of the -- the metabolized dose of MTBE.

One of the things which we did attempt to do -- and this I will explain from -- as part of what's happening in table 11. One of the things we looked at was

the question of whether we could use the concentration of the metabolite TBA as an index of some perhaps more critical exposure than just how much MTBE is around.

The conclusion that we came to was, firstly, subjects of various other discussions in the document, we really don't have any evidence to suggest directly that TBA is the critical metabolite. So it wasn't safe to base a risk-assessment conclusion on that assumption.

And secondly, we do have problems with the model in terms of predicting the TBA concentrations. What this shows in table 11 is that the MTBE C-max and area-under-the-curve predictions between the -- where you've got the observed figures, which are in bold italics, those are actual observations which match to the theoretical values.

And by the standards of these things, the match is considered reasonably good. I think it may be worth commenting that the C-max -- this is the peak concentration achieved immediately after dosing -- is actually a very difficult parameter to model.

It's highly sensitive to all the inputs. And in particular, it's sensitive to details of the exact compartmentalization, and things like differential absorption, and different regions of the gut, and local blood flows, and things like that, which our simple model

simply doesn't accommodate.

So allowing for that known imperfection of the complexity of the model that we're using, I think you would look at the observed versus predicted concentrations as not being too awful for C-max for MTBE.

DR. GLANTZ: So the observed are in light type and the predicted value -- no.

DR. SALMON: The predicted are in bold.

DR. GLANTZ: And the observed values are in heavy type?

DR. SALMON: We have predictions at 40 milligrams per kilograms, which match one set of observed values, and predictions at 400 milligrams per kilogram, which match the second set of observed values. And what I'm saying is, basically, the C-max is, if we're anywhere in the right ballpark, we're actually doing fairly well.

And what we would actually be looking for, which isn't easy to show in a table, but if you -- you know, I mean, the model produces a fat stack of paper as its output. And if you look through that, what we're looking for, in fact, is a reasonable approximation between observed and predicted over a time-course type of experiment.

And what we're saying is, over that time-course experiment, we have a reasonable match. And

in fact, C-max is probably the hardest point on that curve to model. The other one --

DR. GLANTZ: Well, but if you look, though -- I mean, if you look at the 40 milligram per kilogram dose, you're saying that -- you're predicting .068, whatever the units are here.

DR. FUCALORO: What are the units?

DR. SALMON: Minimolar.

DR. GLANTZ: But what you're observing is two or three times that.

DR. SALMON: Well, if --

DR. GLANTZ: And if you go down to the 400 milligram per kilogram dose, you're off by -- maybe a factor of two, isn't so bad.

DR. SALMON: I'm saying for C-max, that is actually fairly good. And the -- the match against the observed profile will actually probably be quite a lot better further out in the curve. But -- so, yeah. That's exactly what I'm saying. That C-max within a factor of two for that is, in fact, quite reasonable by the standards of these things.

The one which is closer to what we're actually using for the -- for the basis of the risk assessment, is the area under the curve, the units of this being millimolar times hours. And the area under the

curve figures -- as you may notice, the match is still not perfect for MTBE. But it is, in fact, quite a bit closer.

And I think given the -- essentially, you could say the parameter we're using for the basis of the risk assessment is -- is closely related to that area-under-the-curve figure. And if we're within, you know, 20 or 30 percent of the right value, bearing in mind that, you know, there's a significant variation between the different experimental observations.

So there's quite a bit of uncertainty in the data here. But in a worst case, we're probably all right within a factor of 20 or 30 percent. Which means that the uncertainties in this parameter are substantially less than the other uncertainties with which we have to deal.

And -- but on the other hand, I would point out, as noted in the document, we're not satisfied with predictions for the tertiary butyl alcohol metabolite. And the reason for this is, there are some compartmentalization and further metabolism issues with TBA, which we have currently insufficient information to make a proper prediction.

And that is one of the reasons why we chose to use the relatively unsophisticated model parameter of simply looking at thing area under the curve to validate the model and predicting the basis -- the dose basis on

total absorbed and metabolized MTBE, which is shown in table 12.

The -- these -- so what we're doing is, we're looking at the model structure, and we're choosing a parameter which we feel we can predict with a reasonable degree of confidence across a fairly wide range of doses.

And we can use that as the basis for our dosimetry and the risk assessment, without making any unsupported assumptions, either about the pharmacokinetics or about the mechanism. That's what we hoped we were doing, anyway.

DR. GLANTZ: Well, so basically what you're saying is, you're within a factor of two. You think that's pretty good.

DR. SALMON: For the -- for the C-max, I think so, yes. I mean, one of the things is, that's an extremely difficult parameter to measure accurately.

DR. GLANTZ: So -- so how much did you -- did you wiggle these parameters around to get that? Or did you -- or did these -- Borgoff and Row and Ginsberg wiggle their parameters to get that fit?

DR. SALMON: We've used a number of different combinations of parameters and chosen, basically, the parameters here. The fact that we were using it -- the V-max values from Row and Ginsberg, and

also one of the partition coefficients from Row and Ginsberg basically reflects the fact that we feel that was the combination of available and peer reviewed and respectable parameters that --

DR. GLANTZ: Now, were those values -- were the data on the observed levels of these parameters, the variables and tables 11, 12, and 13 -- were those involved in deriving the parameter values in table 10 or did the values in table 10 come from independent sources? You plug them into the model, cranked out a set of predictions independent of the data --

DR. SALMON: The essence of this is one should be using externally derived parameters. There are a couple of things like the -- for instance, the gastrointestinal absorption rate, which we simply had no data. So that had to be an assumed parameter, as noted in the table. But --

DR. GLANTZ: Right. But that's a different question, though.

DR. SALMON: But Borgoff and Row and Ginsberg are using externally validated values for their parameters.

DR. GLANTZ: How does that -- how does the data in tables 11, 12 and 13 relate to the Borgoff and Row and Ginsberg models? Did they use the data in 11, 12 and

13 to get their parameter values?

DR. SALMON: They would have used some -- I think that they were actually, possibly using a slightly different subset of the data than -- I don't have that exact information at hand. Certainly they would have been looking at a slightly different combination of inputs. So what we're saying --

DR. GLANTZ: But you took -- I mean, I don't mean to be rude. I'm just feeling kind of pressed for time here. So would I be correct in saying that the parameter values in table 10 basically came from the literature?

DR. SALMON: Yes.

DR. GLANTZ: You took them out of the literature, you didn't do anything to them?

DR. SALMON: We didn't do anything very high-handed. We attempted to make a synthesis.

DR. GLANTZ: Right. But in particular, you didn't wiggle these parameter values to get the predictions?

DR. SALMON: No.

DR. GLANTZ: Okay. Is the data in 11, 12 and 13, the light numbers --

DR. SALMON: Yes.

DR. GLANTZ: Were those values in any way

involved in developing the parameter values in table 10? Or is that subsets of completely independent data?

DR. SALMON: Apart from the cases like the GI absorption, where it's -- has to be used as a model assumption, the parameters of the input and the prediction numbers of the output, it isn't an iterative process.

DR. GLANTZ: Okay. I don't mean to hammer on this. When you're talking about the GI values, you say you assumed those. Okay. You didn't adjust those in order to --

DR. SALMON: We had to figure out what was a reasonable assumption.

DR. GLANTZ: Right. But that's -- there's two different ways you can do that.

DR. SALMON: Yes.

DR. GLANTZ: One way, you can sit down and consult your Ouija board or whatever and come up with what you think a reasonable value would be. And then you take all the reasonable values, plug them into the model and --

DR. SALMON: See what comes out, yes.

DR. GLANTZ: And then -- and you do that. And you take your blindfold off, and you look at what the data is.

DR. SALMON: Yes.

DR. GLANTZ: The other way, you can use the

data to help you estimate what values to use. So would it be a correct statement to say that you didn't do that?

DR. SALMON: We didn't do that. We -- if we found a mismatch between our model output and the experimental data, what we would do is realize that we had a problem and go back and look for better externally estimated model parameters. Not to mess with the values of the physiological parameters in -- inside the model.

DR. GLANTZ: Well, but that -- that seems inconsistent. See, what I'm trying to get at is how, you know -- if you came up with a set of values with a model that was defined independently of the data that you've shown in 11, 12 and 13, and you plug those numbers into this a priori model, and a bunch of parameters that you got a priori from the literature, and then you came within a factor of two to independently observed data, that's pretty good.

DR. SALMON: That's essentially what we're doing.

DR. GLANTZ: Then you went on and said, if the fit wasn't that good, then we went back and reconsidered --

DR. SALMON: We basically, if we saw we had a problem, we would have had to have done something about it. I'm not saying that this is quite -- I mean, this --

as you know, this business of PBPK modeling is somewhat of an arcane science.

But we have -- we have consistently tried to avoid the process which some modelers have used of tweaking the parameters until they get a decent-looking fit. We've tried to use, at all times and whenever possible, to use externally derived and validated parameters.

DR. GLANTZ: But the part I'm still -- I'm hanging up on, I don't mean to just hammer on this. But I mean, you either did adjust the parameters one way --

DR. SALMON: We didn't adjust them. We selected them.

DR. GLANTZ: Well, but that's -- that's the same thing. I mean, the thing that I'm concerned about is, you've got a huge number of degrees of freedom here in this model. And -- and, you know, you don't have -- you're basically trying to predict one number, which is the C-max number. And so I'm a little bit concerned that -- that you can, by turning the knobs on the model --

DR. SALMON: Yeah.

DR. GLANTZ: -- you're going to be able to get the fit, and then you're turning around and using -- so the model parameters are essentially determined by the data you --

DR. SALMON: No, that is not the case.

DR. GLANTZ: But you told me before, though -- this is where you're giving me two different answers. One is you're saying, no, the model is taken a priori. The parameters are taken a priori, and we came within a factor of two. But then you're saying, if we looked at it --

DR. SALMON: If it had been out with a factor of 10, we would have had to gone back to the drawing board and figured out why --

DR. GLANTZ: Did that happen?

DR. SALMON: No, it didn't. Borgoff and Row and Ginsberg both have previous reasonably successful models. We -- we basically used their prior work and selected a combination of what they -- of their conclusions, their model structure, and their parameters to build what we felt was a good consensus model.

DR. GLANTZ: And you did that before you looked at the data in tables 11, 12 and 13?

DR. SALMON: Yes. Then we would have used -- then the process is to validate the model after it's being created.

DR. GLANTZ: Okay. So the data in 11, 12 and 13, there were no adjustments made. Is this a true statement? That after you went through the process of

looking at these published models and coming up with what you thought, in your best professional judgment, was the right model to use with the right parameters. So you did that, and then you plugged it in, and you cranked out a group of predictions.

DR. SALMON: Yeah.

DR. GLANTZ: And then after that was done and those predictions were then chiseled in stone, and those are the numbers in tables 11, 12 and 13; is that true?

DR. SALMON: I believe it's --

DR. GLANTZ: And then after you did that, then you went out and looked at the data that's bold face --

DR. SALMON: Yes.

DR. GLANTZ: -- in 11, 12 and 13? So the numbers in 11, 12 and 13, the bold-faced numbers, played no role whatsoever --

DR. SALMON: No, that's axiomatic. They're not input to the model. That's axiomatic.

DR. GLANTZ: If that's the case, and now I do understand. I mean, I do understand how to read the tables.

DR. SALMON: I have to say that, running these models is a rather messy and approximate kind of a

business. But one does one's best to make an independent --

DR. GLANTZ: Now you're back to kind of waffling. I mean, I -- let me ask --

DR. BLANC: I think, if I could intervene, I think your question has been asked and answered.

DR. GLANTZ: But I don't under the answer. Well, tell me the answer, then.

DR. BLANC: The answer is, they satisfied your requirements, and they did not go through an intergroup process where they kept choosing a better model based on the results that was given.

DR. FUCALORO: Better -- or tweaking of parameters.

DR. GLANTZ: Is that a true statement?

DR. SALMON: Yeah.

DR. GLANTZ: Okay. I'm happy.

DR. BLANC: Verging on asking the questions, are you still beating your numbers?

DR. GLANTZ: Sort of. Every time I thought he said that --

DR. FUCALORO: One science.

DR. GLANTZ: If that's the case --

DR. BLANC: If he said it with a New York accent, you would have accepted it the first time.

DR. GLANTZ: I'm not from New York. Okay. If that's the case; okay -- he is. If that's the case, then I'm satisfied with this. I mean, because I think -- I think to get -- to get from -- you know, if the model -- to get an a priori model to get within a factor of two is, in fact, pretty good. And I think --

DR. FUCALORO: Almost unbelievable.

DR. GLANTZ: Well, not necessarily. I think -- and then I think that -- that the -- that going from there to the oral -- the oral unit-risk number is just pretty straight forward arithmetic at that point. So that to me was the nub of the issue. So I am satisfied with the numbers in the report, then.

DR. FUCALORO: Thanks, Stan. I didn't want to seem like a weak chair, but I realized that you had to go, so I'm going to give you every minute you wanted.

DR. GLANTZ: I'm going to have to leave in about two minutes. I think if the discussion, which looks like it will go on after I'm -- after I have to leave, in terms of the -- my level of expertise and input into this process, I am now satisfied. There may be some other things that other people want to raise.

DR. FUCALORO: Well, Craig is ready.

DR. GLANTZ: Craig is ready.

CHAIRMAN FROINES: The important question

for you, though, because I think that within the context of this room -- and not to take anything away from anybody else -- you're the most familiar with the quantitative issues. And, so remember what I said at the beginning, if you consider this, quote, "sound science," then that's --

DR. GLANTZ: Yeah.

CHAIRMAN FROINES: You need to leave us with your views.

DR. GLANTZ: Yeah, I think it's fine.

DR. FUCALORO: Thank you, Stan. I understand. Craig, did you want to --

DR. BYUS: Yeah, let me go over a few things. I guess I had the most concerns the last time, and I still have them. Just -- and I have another one, which I thought of in their intervening time.

My main concern was over the animal experiments, themselves. Although one thing I have concern over is the performing of the genetic modelling, as well. I was concerned, there's relatively small numbers of animals in most of these studies.

I did have some concern that they were done at very high levels, some of them exceeding the maximum tolerated dose, some of the studies. Which overlays a lot of toxicities on the interpretations of some of the results, particularly the renal toxicity, which I'll get

to in a minute.

Because the compound is a, apparently, quite lethal toxic, no matter how it's administered, probably. So small numbers of animals, the high doses, again, I know that studies are done in high doses. And I'm going to ask you in a minute what was the actual dose extrapolation? How many logs did you actually extrapolate down to ambient? Because it's kind of buried in all the calculations.

That also gives you some idea of how confident you can be in the numbers. There's the one study that has the very sex-specific outcome. I think it was one the leukemias where only female mice got the tumors. And again, that's not totally uncommon. But there was some lack of consistency among the kinds of tumors across the experiment. Some consistency, but there was also some inconsistency.

The other thing from last time was my concern about the dose-response data. We discussed this briefly. Within an individual experiment I'm talking about. Within an individual tumor experiment, did you see a dose response? So as you increase the dose, did you see more tumors? And there is some dose-response data in here. But it is relatively minimal.

And this is also overlaid on the fact that

the significances -- the degrees of significance were calculated, as we went over last time, one-tailed, as opposed to two-tailed. We can discuss this. But this is a one-tailed analysis, not a two-tailed analysis -- okay -- which affects how you want to interpret it. It's not said anywhere in here. That -- you told me that. Or somebody told me that the last time.

So I just -- just as an indication of what -- I mean, about the lack of dose response, you say on page 55 -- you disagreed with me about the statement, so I'm going to read it to you. And I think it's the next to the last paragraph.

> "Despite the reduced sensitivity of bioacid, a statistically significant increase in interstitial cell testicular tumors was observed in mid and high-dose mammals with a clear dose response evident."

Table 8. If you turn to table 8 and look at the bottom, in the testes to the lytic cell, this is not what I would call a clear indication of a dose response. I mean, I just don't think the data states that. Okay. So that is the kind of concern I had.

Now, the last concern I had, in addition to the fact there's no human data and there's no clear mechanism. And again, it's -- you did a very nice job

trying to come through, figure out a mechanism, but there really is no clear mechanism.

But my last concern, which I didn't discuss last time, has to do with the clearance. If this is a fairly renal-toxic compound -- and according to your paper -- I mean, to this document, it's very renal toxic -- all treated mammals, both female and male rats, had a progressive, chronic nephropathy, all kinds of changes in kidney function. Mid, high dose, is where it occurred.

"Mineralization and interstitial fibrosis of the kidney, which increases in mild to moderate" -- oh, I'm sorry. Sorry.

"Mineralization and interstitial fibrosis of the kidney while increases in mild to moderate glomerulosclerosis, interstitial fibrosis, and tubular proteinosis were observed in females."

So my last point is, if this is a really renal-toxic compound, which it is, what is happening to the pharmacokinetics in these long-term tumor experiments at the high doses? Since this compound is cleared both the parent compound and the metabolites by the kidney, what's probably happening, as you increase the dose and as you give it over time is, the kidney's becoming damaged.

And so the metabolites might be building up to very high levels. The parent compound might be building up to really high levels. And so you probably have a much higher real dose than your externally applied dose.

And your pharmacokinetic modelling doesn't really take that into consideration. It takes it into consideration, I believe -- and correct me if I'm wrong -- just for an acutely administered dose, not the chronic, two year or year and a half, whatever, where kidney damage would be occurring.

So again, I mean, I think the data is there. I do believe that it is a carcinogen that is causing cancer in animals, clearly. But all these concerns, you know, I start thinking about a threshold-type mechanism, et cetera. So I mean, there -- that's -- I'm done.

DR. SALMON: Okay. I will comment on a couple of these issues. And I think I will then hand over to my colleague, Dr. Sandy, to address some of the others. If I can take your last point first about pharmacokinetic model, it's certainly true that the pharmacokinetic experiments are single-dose based.

So if there is accumulating damage, then the pharmacokinetic model will fail to reflect that. I'm not

sure that we can -- I mean, one of the problems, of course, is that we're entering the realms of speculation as to how substantial that effect might be.

If the -- for the sake of argument, the clearance of MTBE were to be reduced by a factor of 2 or something like that, then obviously that would be seen as fairly significant in terms of an impact on renal function. But I don't think that it would make an enormous difference to the -- either the qualitative or quantitative conclusions that we would be able to draw from the data.

If the impact on kidney function were much more severe than that, then it's -- I would imagine that you would be getting into the zone where the kidney damage would be fatal, which may well have occurred with some of the animals. But of course, at that point, they cease to play a part in the study anyway. So they would not be impacting the result.

But I would -- basically what I am saying is, I agree with you that this is an uncertainty in our conclusion, and we have been at some pains to point out that there are a number of considerable uncertainties in the conclusion.

But we've done our best to work through what information we did have, and could interpret. And

basically to follow -- follow our guidelines in determining an appropriate and public-health-protective level, in spite of the uncertainties. I think that's all I'm -- I'll say.

DR. SANDY: And I'll address a few points. Animal bioacids, in general, that are conducted now, for example, by the National Toxicology Program, which is considered the gold standard for design, it's 50 animals per group, per sex. And that's what was used in the inhalation studies for the rat and the mouse, and for the Gavage studies, they used 60 animals per group, per sex.

So I would not characterize those as small numbers. Those are -- those are the numbers that we work with when we look at animal bioacid data, if we're lucky. Small numbers is 20, and that's from historical studies.

We do acknowledge that, in the rat-inhalation studies, MTBE was renal toxic. And, in fact, the study pathologist, as well as -- I guess had a second pathologist look at the slides, confirmed that MTBE seemed to exacerbate the chronic, progressive nephropathy seen in rats of both sexes. So that is something that is going on. You're correct.

There are a number of carcinogens -- kidney carcinogens which are also nephrotoxic. And that's just something that we'll have to deal with. As Andy said,

it's part of the uncertainty. Let's see. For the dose response, we do see a dose response in the combined incidence of lymphomas and leukemias of lymphoid origins in the female Dawley rats used in the Gavage study.

The incidence that was reported in the 1998 pathology review by Belpoggi was 3.4 percent in the controls, 13.7 percent in the low dose, and 25.5 percent in the high dose. Now, only the high dose was statistically significant. And we did not do a trend test, because this data -- the authors of the paper, they did not analyze it using a Fisher exact test. They analyzed it using a log rank test.

DR. FUCALORO: Using what?

DR. SANDY: A log rank test. And that entails having time-to-tumor information, which we could not obtain, so we could not replicate that analysis. We just took the data and did a Fisher exact test, which is one-tailed. And that is, again, a -- the accepted, common way of analyzing animal bioacidic data.

DR. BYUS: We just repeated this the last time.

DR. SANDY: Well, so --

DR. BYUS: That's okay. But in any case, you should indicate one-tailed versus two-tailed. It should be stated what statistical test you're using,

clearly.

DR. SANDY: Again, just like to emphasize, the data was analyzed by the study authors by another method. And it was also significant, the incidence of the high dose.

DR. BYUS: The incidence of high dose or the dose-response relationship?

DR. SANDY: The incidence of high dose. In the -- the male Fischer rat -- that's the inhalation study -- the -- that's table 8. The tumor incidence for testicular tumors, 64 percent of control, 70 at the 400-parts-per-million dose, 82 at the 300 -- sorry -- 3,000-parts-per-million dose, and 94 percent of the 8,000-parts-per-million dose. I believe that's a dose response.

Again, this study had early mortality in the mid and high-dose groups. So you're seeing -- you're still seeing a dose response, even those these animals are dying sooner.

DR. BYUS: I know I would never call that a clear evidence of a dose-response effect. I mean, I would say that is very weak evidence if -- at the best. I wouldn't call this a clear-dose response.

DR. MARTY: Craig, is your concern that high incidence in the controls -- is that part of the issue?

DR. BYUS: That is part of it, sure. Of course. Plus, if you factor all of this in, the variability of the control incidence and the cross studies, the very incidence of it, which as I said last time is -- what you're probably doing is simply affecting time-to-tumor, rather than actually affecting the overall incidence.

And I don't want to argue -- you know what I mean -- about that. What that means -- what the significance is. But I would not call this a clear evidence of a dose response -- tumor-incidence dose response.

The reason it's important, of course, is whether or not there's a threshold. I mean, that's the point. That's why seeing a clear evidence of a dose response is important, in a sense. You see what I'm saying? Clear evidence.

DR. MARTY: I think it's -- we should point out that at the mid and high dose, those were both significantly different than control. So it may -- maybe is a semantic issue versus a clear --

DR. BYUS: I teach pharmacology to the medical students. I also do tumor studies where we try and establish a clear dose response. And that is different. Yes, they may be different than control. But

it is not indication of a clear dose response, I mean, in my opinion.

DR. BLANC: Well, perhaps what you're trying to say, there's a difference in a qualitative statement saying that the data can be interpreted as showing a dose response, versus the implication that there is statistical relationship between the group suggesting a step up, in effect, or consistent with it.

And so it sounds, if I see -- hearing the difference in the two points of view, you, from a qualitative point of view, felt the data consistent with the dose response. But there isn't a statistical test that you can state you performed that's consistent. In the one case, said you couldn't do a test of a trend because of the way the data was presented. And in the latter case, was there indeed a test for trend?

DR. SANDY: I think we can and probably should have done a trend test. I would --

DR. BLANC: Because I think --

DR. SANDY: -- hazard to guess it would be significant.

DR. BLANC: Well then, I would suggest you do that. And I think that that -- and then rather than get hung up on, you know, one man's meat is another man's poison, you simply say that it was a statistical

relationship that was consistent with the trend.

DR. SALMON: One of the other things is that I think, for the purposes of our risk assessment, which is, you know, essentially what we're looking at here, we were concerned to follow the letter, both of our assessment guidelines, and also the Health and Safety Code applicable to the TAC program.

And I quote, "Where it can be established that a threshold of adverse health effects exist, the estimate shall include a appropriate factor." Our risk assessment assumptions would only consider a threshold analysis if there was solid evidence for a threshold.

DR. BLANC: Which there isn't?

DR. SALMON: Which, I think, regardless of which side of the fence you come down on -- I'm sensitive to the fact there's a debate here, obviously. The point is, either way you think about that debate, I don't think you could argue that there is any substantial evidence for a threshold. Or at least, that was the interpretation which we made when we undertook the risk assessment.

DR. BYUS: It's mainly -- it's mainly the language. It seems -- in my opinion, it seems to be overstated in the document. That's all I'm getting at.

DR. SANDY: Okay.

DR. BYUS: I don't disagree with the

conclusion that this is a carcinogen or causes cancer in animals, clearly. I'm just disagreeing with some of the language, in my opinion, tends to be overstating the animal data.

DR. FUCALORO: I do want to point out, the issue is not whether -- the only issue is not whether it is carcinogen -- whether it's carcinogen or not. What I think we are charged to do is to come up with a potency factor. And I think that -- and your comments really address that issue. And I think that's something -- something we need to discuss. I don't believe they answered your first question regarding how high these doses were.

DR. BYUS: The extrapolation. How many orders of magnitude did you extrapolate?

DR. FUCALORO: I think you used the words "logs." Orders of magnitude; right?

DR. BYUS: What is the extrapolation here?

DR. SALMON: We don't actually make an -- such an extrapolation in the document. Because, of course, we're not saying that, you know, there is a specific exposure level to MTBE out there, which we're trying -- which we're evaluating at this point.

However, I think it would be fair to say that, taking the typical ambient levels of MTBE which are

out there at the moment, it's something around 4 or 5 orders of magnitude, which is not untypical for the sort of extrapolation --

DR. FUCALORO: So 4 or 5 orders of magnitude greater than what is --

DR. SALMON: Than what is ambient, yes.

DR. FUCALORO: 10 to a 100,000 times more?

DR. SALMON: I believe that's correct.

DR. BYUS: We have put that in documents before. First document I ever did, which I can't even remember what the chemical is now. We did, in fact, say that we extrapolated 5 orders of magnitude. It's just something that, you know, especially -- again --

DR. MARTY: I think we can add that. We can add that to our attachment, based on the information we get from ARB regarding concentration of air.

DR. BYUS: I know. And I understand what you've done. And I understand the quantitative risk assessment, and what you're trying to do. But, I mean, in a sense, we're talking about mechanism. In a way there's -- you're trying to interpret -- trying to put some substance on some kind of mechanism and validity. And really the further -- I mean, it troubles me that we're extrapolating 5 orders of magnitude for this number.

DR. MARTY: I would agree.

DR. BYUS: It always troubles me when we extrapolate 5 orders of magnitude or 4. Much better if it was one order.

DR. MARTY: Yes, I don't think we would disagree with that at all.

DR. BYUS: No one would disagree with that, I hope.

DR. SALMON: It's just we don't have the means to do anything else.

DR. BYUS: I know. I'm not saying you should have the means. It's part of the, in a sense, the language here.

DR. SALMON: Characterizes the uncertainty.

DR. BYUS: Characterizing the uncertain, exactly.

DR. BLANC: You know, I have a solution to this. Because, if I understand what we're being asked to do, we're being asked to make our finding, in light of their document -- which once again, I think would be some kind of written memorandum, not of great -- or are we just being asked to make sentence --

CHAIRMAN FROINES: We're being asked to vote on whether what they've done is sound science, period. There will be no finding on this.

DR. BLANC: There's no finding? Are we

asking -- and the attachment of health effects of exposure to methyl tertiary butyl ether, is that the only thing we're commenting on or commenting on the entire document? How does this relate to the entire document? As an addendum to it?

DR. MARTY: Can I --

CHAIRMAN FROINES: We're voting on that document.

DR. BLANC: Not on this. What is this?

DR. MARTY: Can I drop in here maybe a little bit? When we were asked to come up with the unit risk factor by inhalation exposures by the Air Resources Board, we had just completed a document to our public -- our Public Health Goal Drinking Water Program.

So we took that document and used the information in there, and had to do some more calculations to get to the dose via inhalation -- target dose via inhalation, and then back to a unit risk factor for use with concentrations in air. That little end piece of it is what is attached to the attachment. In terms of commenting on the PHG document, you know, you guys needed to see that because --

DR. FUCALORO: This document?

DR. MARTY: Right.

DR. FUCALORO: This is the document where we

have to render judgment on whether or not --

DR. MARTY: And you need the bigger document in order to understand what we've done in the little document.

DR. BLANC: So this is actually what we're commenting on?

DR. MARTY: Right.

DR. SALMON: We don't have a mandate to modify the PHG document at this point.

DR. MARTY: Right. We can't modify this document. But we can address your concerns by putting information into that appendix.

DR. BLANC: But wouldn't that delay the whole process? You have to come back to us again.

DR. FUCALORO: That was -- I was going to -- do you need to come back to us again or is it possible for to us vote now? I'm not clear -- I'm not clear on that. Craig brought up a lot of -- many points, and there was some disagreement and some agreement, I think, on the points he brought up. What do you -- what do you suggest at this point?

DR. MARTY: Well, I would suggest that we modify the little document to address the uncertainty issue, which is what Craig was getting at. And then --

DR. BYUS: That's clearly all I'm getting at

is clearer explanation on the uncertainties, not on the overall process. Because you did a very good job. It's just at the level of the uncertainties.

DR. BLANC: I would say its fine if you do that. I would also say, if I understand the charge to us, if the charge to us is to comment on whether what you did is consistent with standard and acceptable scientific process, then I think, it's about as easy as saying that diesel exhaust is toxic air contaminant.

Which is -- that's kind of a no-brainer. Of course it's a toxic air contaminant. And, you know, yeah, you dealt with the uncertainties that we deal with every single time you have to do on these exercises. But what you did is what is standardly done.

I really think that the discussion is -- because it's so applicable to every single one of these cancer-potency things we have to deal with. But on the other hand, I don't think it would, in any way, make me say that this wasn't consistent with standard practice. All the more so. So I would certainly feel comfortable just calling the question.

DR. FUCALORO: Well, I think -- jumping ahead. I think, though, I'd like -- I think give everyone an opportunity to comment, because we certainly asked Stan to comment, and Craig. And there may be no other

comments. I mean, I frankly -- I think Craig and Stan -- I made my comments, I feel. Roger?

DR. ATKINSON: I have no comments.

DR. FUCALORO: John, did you want to say something on this? Yes, he did. But he won't.

CHAIRMAN FROINES: Maybe I'll let it go. I think that the -- I think Craig's comments are very useful and valuable. I think that we have to keep fighting the tendency on, where does the burden lie on these things.

And that is, it is not -- the burden is not up to the state to demonstrate mechanistically the relevance of animal-cancer data to humans. I take that as not being the burden of the state. I take it as the burden of the critics to demonstrate the irrelevance of the animal data.

DR. BYUS: That's right. Very good.

CHAIRMAN FROINES: And there are enormous difficulties with MTBE. There's no question, whatsoever, that there are scientific difficulties. But the conclusion that we came to was that we found no evidence to demonstrate the irrelevance of lytic cell tumors or liver tumors, what have you, even though we didn't like lots of stuff about that science.

But it's this notion of who has the burden, that I think is really quite important. The other problem

is, the two inhalation studies were done by industry. And they have the most problems, in many ways, in my view. They're the ones with real toxicity problems, so on and so forth.

And we find ourself in this very strange position of having industry studies, which we criticize. And if we don't then accept the positive findings, we, in a sense, are rewarding the people who did the bad studies. So that's really contradictory in terms of the way we have to look at it, it seems to me.

And the other thing is, that if this was an abstract question, we really could debate it. But it's not, because we have 15 percent of the stuff in all our gasoline. So actually we're breathing it as we speak.

So I frankly -- frankly, as far as I'm concerned, this is not a quantitative issue. It's a qualitative issue. I would rather not have this in my gasoline, as a qualitative matter. So I agree that you want to do reasons that I don't even understand the quantitative risk assessment. That -- seems to me, that's not even the issue here.

The issue is, the government should never have pushed this. We shouldn't be in this position in 1999 arguing over an EPA decision from 1992. And this is a bad -- was a flawed policy decision to begin with. It's

still a flawed policy decision. And I think there's light at the end of the tunnel, so we should proceed with it. So it becomes, for me, at some level, sort of a no-brainer --

DR. FUCALORO: All right. Paul, did you want to comment further? How about you, Hanspeter? Then I would ask the panel. This is the pleasure of the panel to make a motion that I will suggest in a moment, to essentially have closure on this issue.

Is there anyone who objects to that? If not, let me make a suggestion at a motion. I won't move it. I'll allow someone else to, because I have the language here.

> "That the -- this panel finds that this document titled, 'Attachment 1, Health Effects of Exposures to Methyl Tertiary Butyl Ether, MTBE' be found to have sound -- be based upon sound, scientific knowledge, methods, and practices."

And the record shows that John Froines is still with us. I need to say that parenthetically for matters of quorum. And that we -- that's finding one. And finding two, that we recognize that OEHHA may wish to expand upon the document at a future time for purposes of clarity; okay, and to introduce more pertinent information for the purpose of clarity.

Let me stop it there. That's a motion I suggest. If anyone thinks that's a good motion, I will entertain that motion from the floor.

DR. BYUS: I so move.

DR. FUCALORO: Is there a second to that?

DR. BLANC: Second.

DR. FUCALORO: Is there any further discussion on that? Hearing none, I will take the vote. All in favor please indicate by saying aye.

MEMBERS OF THE PANEL: Aye.

DR. FUCALORO: Opposed? Anyone wishing to be recorded as abstaining? The motion carries unanimously. With that, I leave, and turn back orders to Dr. John Froines.

CHAIRMAN FROINES: You know, the tragedy of this thing is, the --

DR. BLANC: John, I suggest we let our stenographer take a break.

CHAIRMAN FROINES: Let's take a ten-minute break.

(Brief recess taken.)

CHAIRMAN FROINES: Okay. MITC. We are back in business. And then, Melanie, we're going to get to the REL. We're going to finish. It will go fast, I think. No, no. They may not. I don't want to -- I realized

who's doing them.

DR. FUCALORO: Don't forget it.

CHAIRMAN FROINES: Forget I said anything about it.

DR. BYUS: He knows too much. He knows too many things.

DR. FUCALORO: You know too much.

CHAIRMAN FROINES: Andrew, please go ahead.

DR. RUBIN: Are we looking at a finishing at 3:00 o'clock?

CHAIRMAN FROINES: No, go ahead. We don't have any --

DR. RUBIN: Okay.

CHAIRMAN FROINES: We'll all try and push this panel along. You work at your pace.

DR. RUBIN: All right. First -- first slide. Let me just start, before the first slide, which is -- has my name on it, basically. My name is Andy Rubin. I'm the staff toxicologist at DPR responsible for the risk assessment on MITC.

In opening up the subject of the assessment of MIT's health effects, I really wanted to be clear from the outset that there are some very interesting problems in determining the critical end-point values. These relate to the significance of the actual end points.

That is, the toxicological effects that were observed, the quality of the studies used, the availability of the sufficient number of studies, and the issue of assigning a subchronic NOEL value that is higher than a -- an acute NOEL value. Which goes against sort of standard toxicologic dictum.

And I'd like to ask for and recommend that the panel, as you read the document, consider these issues that I bring up as we get to them, and as you read the document and critique the document. We're not to the slides yet.

MS. WALES: Technical problems.

DR. RUBIN: The slides are so amazing that they've broken the overhead projector.

DR. FUCALORO: Is it on?

DR. BYUS: It just started.

DR. FUCALORO: Let the record show it was my finger that -- dumb luck.

MS. WALES: It's on.

DR. FUCALORO: We'll be impressed with this high technology.

DR. RUBIN: I could hold it up, but I don't think you can see it. You actually have copies of it.

DR. FUCALORO: We actually all have the copies of it.

DR. RUBIN: There we go. There's something -- yeah. Okay. This is an overview of the subjects I'd like to cover. First, the Cantara Loop spill, which I'll explain in a minute. Little bit about the pharmacokinetics of MITC in mammalian systems.

Then on to the acute toxicity, subchronic toxicity, chronic toxicity, oncogenicity, and the famous DPR margin of exposure calculations, reference exposure level concentrations, and the possibility of toxicity due to other Metam-Sodium breakdown products. In particular, methyl isocyanate and hydrogen sulfide.

Next. Any consideration of the potential human health impacts of MITC must or should begin with the realization that we actually have some real-world human toxicity data out there, courtesy of the Southern Pacific Railroad.

Back on July 14th, 1991, a train -- a mile-long train heading north near -- about six miles north of the town of Dunsmuir couldn't quite make it up a grade. Some of the cars skipped the track, and a tanker car containing 19,500 gallons of 32.5 percent Metam-Sodium went into the river.

In the hour or two after -- within the hour or two -- within the next few hours after that accident occurred, it was felt that there was only a breach above

the water line that was soon dispelled -- to dispell within 12 hours when it was learned that all 19,500 gallons had gone into the river.

And this map just -- this, by the way, much of the data -- very creditable data comes from OEHHA and DHS's assessment of the health effects of this spill. And this map simply shows -- you probably can't seen see it too well. But basically the Sacramento River with the railroad running next to it.

And right up at the top there -- do I point this or -- okay. There it is -- is the Cantara Loop, which is a -- which is a loop that goes up a grade. There's a bridge over the river here. And that's where the spill occurred. This occurred at 9:39 at night. By 9:15 the next morning, the plume of Metam-Sodium -- the big green plume had run by the town of Dunsmuir where the major exposures occurred.

That's probably the major population center near the spill. Population of about 3,000 people. Had run down and had reached Castle Crags. Basically by the -- by the morning of the 17th, three days later -- two and a half days later, say, the plume was emptying into Shasta Lake.

The primary human exposures, as I've -- as I said, probably occurred in the town of Dunsmuir. Now,

the -- from a toxicological standpoint, we're very interested in what the levels of -- of exposure to MITC were in the town of Dunsmuir near the river so that we can gauge what kind of levels caused what kinds of effects.

Unfortunately, it wasn't until three days after the spill that good, reliable monitoring was in place. Consequently, in the modelling that -- consequently, the levels of Metam-Sodium had to be estimated based on environmental-fate and transport modelling.

Actually, there were a couple of models that were used to estimate the air concentrations of MITC around Dunsmuir after the spill -- after the spill. One was an environmental-fate and transport model that took into account the evaporation rate, the amount of sunlight, the wind, the meteorologic conditions and so forth, as well as the known physical, chemical properties of Metam in water and how it breaks down to MITC, and how fast MITC will go from a water phase into a gas phase, and so forth.

Another model relied on measured concentrations, concentrations that were measured three days later in the river, and compared them to measured concentrations in the air. Basically, a ratio was set up. So there were two -- there were at least these two different models, and some variations in between.

The only reason I mention this, is that there are some estimates of the levels of MITC in the Dunsmuir area soon after the spill. Within -- but please recognize that these are only estimates. These are not measured values. Actually, there are one or two people in the room who actually did these studies, and I want to recognize that they are here.

In the 4 to 12 hours after the spill, the maximum estimates, based on the model and the assumptions used, ranged from a hundred and forty to 1600 ppb. Between hours 12 -- and these are -- these are levels that were at the river. At hours 12 to 24, we're dealing with 88 to 200 ppb. And at 24 to 48 hours, we were dealing with 15 to 88 ppb.

These are very important considerations in -- in this risk assessment, because we have to consider not only -- we have to consider the whole spectrum of toxic effects that occurred there. When we're looking at a laboratory assay that may only be measuring one toxic effect.

In other words, as you'll see on the next slide -- I don't know if I made clear, but the next slide shows that there are -- there was a whole plethora of toxic effects that were detected, mostly in the town of Dunsmuir following the spill. And this is all from

OEHHA's publications on the issue on the spill.

There were 848 spill-related hospital visits from 705 separate individuals in the month following the spill. These are the effects that people were reporting. Headache in 64 percent of those visits. Eye irritation in 49 percent. Throat irritation in 42 percent. Nausea, 46. Dizziness, shortness of breath, diarrhea, nasal irritation, and chest tightness. These were the -- I only listed on this table the most commonly expressed toxic effects.

There were seven hospitalizations, four people with respiratory problems. Two with fainting problems. One person with disorientation and irregular heartbeat. And according to the paper -- one of the papers, that person may have received an excessively high dose. None of these are known for sure, though.

There were eight -- we know about eight exposed pregnant women. Two of them were exposed during the first trimester, and they opted for abortion. Particularly sad outcome to this accident. Four exposed during the second trimester were advised that their pregnancies were progressing normally. I assume that that probably came from their doctors.

DR. FUCALORO: Follow up -- was there follow up on that?

DR. RUBIN: I believe that's the extent of the follow up, at least in the published literature. There was some evidence for the initiation of or exacerbation of asthma over the longer term. And this is a syndrome that was recognized in 1985 associated with exposures to other isocyanates. Syndrome known as RADS or Reactive Airways Disfunction Syndrome.

There were, I believe, oh -- there were 30 -- 30 of 197 adults referred to health practitioners for spill-related reasons, were considered positive for RADS.

DR. BLANC: Can you tell me where, for example, in the document -- in the draft document those data --

DR. RUBIN: Yeah.

DR. BLANC: Because it's not in the acute toxicity piece.

DR. RUBIN: Right. It's before it. The acute toxicity deals with the laboratory studies.

DR. BLANC: It also talks about the Plutara incident. That's why I was confused.

DR. RUBIN: Maybe I've got things mixed up. Page 16, 17 and 18 is the discussion of the Cantara spill.

DR. BLANC: Okay. Great.

DR. RUBIN: So RADS is a syndrome that is a

little more disturbing, because it implies that there may be longer term effects from acute exposures. RADS -- the criteria for RADS include onsets of symptoms within 24 hours of a single exposure, persistence of such symptoms -- and by "symptoms," I'm talking about asthmatic-types of symptoms, dyspnea, wheezing, air-flow obstruction that may be measured in standard spirometry assays in a lung-function lab.

And the possibility that there's sensitization later on. In other words, that a person who's experiencing this -- this syndrome, may have an exacerbation of the syndrome on subsequent exposures to much smaller amounts. I think this is really important. But it's not well-characterized in this particular incident. But it is, at least, a possibility.

We know of at least 30 people, however, that were positive for this syndrome after the Cantara spill. One more issue, and this took a little bit of digging on my part. There were three railroad workers that were dispatched into the spill area within a few hours of the spill by their employers -- by Southern Pacific.

They came in to pull the -- the salvagable part of the train out of there. And they went in there, and they were -- well, let me start this by saying, this does not appear in the scientific literature or in the

medical literature. It appears in a 1997 article in the Sacramento Bee. I did some calling around to some people at OEHHA. And one psychologist that had worked on some of the --

DR. BLANC: I hope it wasn't Rosemary Bowler.

DR. RUBIN: It was. I called her. She had no information about this. It was simply a Bee article on the three guys running a locomotive in there to try and pull out this mile-long train, salvage what they could of it.

And while this is not something that I would perhaps base an entire risk assessment on, a newspaper article, I wanted to recognize that there were three -- three workers that claim, six years after the spill, to have experienced quite a number of symptoms. Permanent neuropsychological damage, RADS, irregular heartbeat, low blood oxygen, coughing, depression, coughing fits, back-to-back colds, loss of drive, peeling away of mucous membranes in the mouth.

I'm not sure how to -- how to assess that kind of thing. But I think it should be brought to the attention of the panel, and it's in this document referenced, the Sacramento Bee, 1997. So --

DR. BLANC: Well, I think -- I think what

you'll hear from the panel, is that section should be excluded. And the -- in fact, the most salient and documentable issues of the respiratory complaints, at least one, and perhaps all three of those people were included in the paper by Cohn, et al. And so you've already included the respiratory findings.

DR. RUBIN: Yeah.

DR. BLANC: And I would probably also say that, I don't disagree with you that the issue of Reactive Airways Disfunction Syndrome and irritant-induced asthma is an important end point in acute --

DR. RUBIN: Assessment.

DR. BLANC: -- acute exposure. And acute-exposure outcome, that's important, and very well-documented from the Plutara spill. But I don't think you need to include, you know, newspaper account where it gets into some of these other very nebulous and probably unsupportable issues of subjective, neurological --

DR. RUBIN: Agree.

CHAIRMAN FROINES: We need to remember that this is the day in which we're having a staff presentation, and then we're going to have a full panel discussion later. So I -- I'd like to give him -- the time is moving on -- to try and move ahead with the presentation and not --

DR. BLANC: Get into the details.

CHAIRMAN FROINES: Doesn't preclude discussion, but it --

DR. RUBIN: Okay. Well, let's move on from the -- from the Cantara incident to what we know from laboratory investigation of MITC's toxic end points. First of all, as far as pharmacokinetics are concerned, all we have is oral-exposure pharmacokinetics. That is, exposure of rats to label MITC via the oral route.

We do not have exposures via the inhalation route. We can say that using doses of 4.433 milligram per kilogram radio label MITC, that 88 to 96 percent was absorbed within the hour. 80 to 82 percent was excreted in urine, and small amounts were excreted in the feces. 6 to 15 percent in the expired air CO2, and less than 1 percent is carboneal sulfide or carbon disulfide within 24 hours.

There was at the end of a week, 168 hours, 1 to 3 percent remained bound in tissues. There -- MITC is conjugated and is excreted as cysteine conjugates, about which, nothing is known toxicologically.

The acute toxicity and the bulk of the toxicity that was observed at Cantara had to do with the irritative capacity of MITC. Oral presentation of MITC to animals always or generally results in irritation of the

stomach lining, the esophagus, and so forth. I'm not going to cover those.

What I'm going to concentrate on now is the acute toxicity via the air, because that is where we think virtually all the exposure to MITC is coming from. When OEHHA did their original risk assessment on the spill -- and indeed, when DPR did a conditional risk assessment in 1994, the only study we had available to assess the toxicity of MITC came from the Ukraine, what we call the Ukrainian Cat Study by Nesterova.

We feel, and I have felt, that this study was so bereft of experimental and analytical detail, that it is virtually unusable. So we got -- we have another study. Another study came along in 1996, an eye-irritation study which was a rather careful study that characterized the chamber -- exposure concentrations and the end points rather carefully.

And I think we can -- well, I will make an argument that this is an appropriate, acute end-point study. This was a human study done in Sacramento -- actually, at UC Davis Medical Center -- in which there were 70 subjects, 38 males, 32 females, mean age of 32 years were the range, from 18 to 67 years old.

And they were exposed to gaseous MITC through specially fitted goggles. Pam, if you put the

next one up there, you get a sense of what it looked like.

DR. SALMON: That slide's not --

DR. RUBIN: It's not in there? Oh. Okay. Well --

DR. BLANC: It's okay. We'll take your word.

DR. RUBIN: They were goggles. They were airtight around the seam. They were fed by a feeding tube and a distribution manifold across the top. When the study was originally commissioned, DPR was approached as to what end points they should measure.

They originally wanted to put a mask on the subjects. And what I am told by the person who initiated this risk assessment was, "No mask here. The pulmonary end points are serious enough that we don't want human subjects breathing this stuff." So all we have from the acute -- from this experiment is an eye-irritation end point.

DR. BLANC: Isn't there -- just as an aside. I hope this doesn't violate your guidelines. But I always understood that one of the issues with the Cantara spill and the immediate health-risk assessment was, that it was a licensed pesticide, and there was pesticide-toxicity data other than just the Ukrainian Cat Study that was deposited with the Department of Pesticide Regulation, but

unfortunately, none of that data was available for anybody's health review. Or is that not true? How did it ever get licensed without any submission of any data?

DR. RUBIN: Well, the spill, I'm -- first of all, I'm not sure I can answer that question, as to what data were available.

DR. BLANC: I mean, are there data relevant to its pesticide registration which is not otherwise in the public domain that you have also evaluated for the purposes of this risk assessment?

DR. RUBIN: Definitely.

DR. BLANC: Does that predate --

DR. RUBIN: Some of it, yes. It does predate the spill.

DR. BLANC: Okay.

DR. RUBIN: In fact, you will notice when you read -- I know this has been at issue before the panel in the past. There are very few open literature studies on the toxicity of MITC. There are a few, and many of them come from the spill and human -- human exposures. But we're dealing mostly with contracted studies.

The human eye irritation study, 70 people exposed for -- just to the eyes through goggles for 14 minutes, 4 hours or 8 hours. They were sitting at tables, and they had a little graph next to them, so that they

could put on the graph a little mark as they felt some level of irritation, say between zero and a hundred. And they would put a little mark on.

That is a subjective sort of semi-quantitative, at best, level of assessment of eye irritation. That -- that technique is called -- is known as the Likert technique or the Likert scale. It's a subjective technique for assessing eye irritation.

There were a number of other end points that were used, including blink rate, tearing, visual acuity, and photographs of the eye. By "visual acuity," I mean put your hand over your right eye and tell me if you can see the chart. And photographs of the eye meaning, before and after, how red were these -- how red were the eyes of these people.

Results were, the Likert scale measurements indicated there was an irritation response at 800 ppb after one hour of exposure. Blink rate indicated an irritation response at 800 ppb after two hours of exposure. There were no -- none of the other three parameters exhibited positivity.

The other factor that is of interest is that, when the subjects were withdrawn from the stimulus, the -- their perception of irritation and their blink rate went back down very quickly. We have -- we have decided

that this was an adequate study to assign a LOEL value of 800 ppb and a NOEL value at the lowest concentration tested of 220 ppb.

CHAIRMAN FROINES: Why don't you skip to the studies that form the basis of the NOEL and LOEL.

DR. RUBIN: Okay. This was the first one. This is the acute critical NOEL.

DR. BLANC: This is the acute one. The next one is going to be subchronic.

DR. RUBIN: I'm actually only going to talk about those studies. Moving on to subchronic. We're dealing here with a 12 to 13 week, 4 hour a day -- 5 days a week, nose only, inhalation-exposure experiment. This one came from Germany by Ross Kamp, et al. First I'll tell you a little bit about what they observed. Then I will attempt to go into some of the weaknesses of this study.

There were ten rats per sex, per dose exposed to 0, 1, 10, or 45 ppm MITC. Clinical signs at the high dose -- and the signs I've listed here in the symptoms I've listed here are ones that were observed in many of the animals at this dose, not just one animal. Included apathy, increased salivation and nasal discharge, vocalization -- vocalization we usually take to mean that those animals are uncomfortable. They want out.

Also body-weight gain was 37 and 53 percent male and females of the sham dose controls. Turns out to be important, because sham dosing itself in this experiment is really hard on these animals. At 10 ppm, which is where we assign the LOEL, we're dealing with much-less overt toxicity. We have decreased body-weight gain, compared to sham dose controls, 89 and 85 percent of sham dose controls in males and females, not statistically significant.

However, I felt that, given the much greater decrement in weight gain at the next higher dose -- at the high dose, that this was a real effect. It can be argued, though, that the lack of statistical significance is problematic. There was also, interestingly, increased water consumption at the LOEL dose of 10 ppm, about 15 percent above sham controls. This was statistically significant.

However, at the high dose, there was also about a 15-percent increase, but it wasn't statistically significant. And there was no dose response. So, that's possibly a problematic end point. I have considered it as a positive toxicological end point.

There was a slight statistically significant reduction in serum total protein. Those are the three end points that we are basing the subchronic risk assessment

on. So one needs to examine the toxicologic significance of these end points, the fact that there's no dose response in this for the increase in water consumption, the possibility that the effect on serum protein may be related to the increased water consumption.

I would say here, parenthetically, that you can find when you feed MITC to rats, and their water consumption actually decreases, because the water that the MITC is in tastes so bad, that they don't want anything to do with it.

But under those conditions, you get drops in serum protein as well. Which made me think that it is at least possible that the drop in serum protein was not related to the increase in water consumption. There was also no histological examination of the nasal cavity. And for an irritant as powerful as MITC, you should be looking at the nasal cavity, the trachea, for irritation effects.

Finally, there is insufficient analytic data in this experiment. First of all, there's no report of daily levels of MITC. This is a difficult thing to do for 13 straight weeks, to put into a -- an inhalation chamber exactly the same amount of MITC every day, and to measure it, and to express those results in -- in interpretable fashion.

What these investigators did was simply add

up all the data that they had, which they did not supply, and give us a mean value. So the implication of that is, that we don't really know what the excursions of the MITC levels were in those experiments. And those, say, at the high dose where the mean value was 45, maybe it went down to 10, and maybe it was occasionally -- and maybe it was up at 165, but we just don't know.

And those are some of the weaknesses in this study. When you don't know the daily doses, what those animals are daily exposed to, and you don't have daily toxicologic data, you can't really tell what the animals are responding to.

But -- and here's -- here is one of the problems that we're dealing with with MITC. This is the extent -- this is really the extent of the studies that we have. And so I feel that, given the overtness of the -- of the response at 45 ppm, and the admitted marginality of the responses at 10 ppm, that that is good enough to call 10 ppm a LOEL dose. Moving on. Okay.

DR. FUCALORO: The LOEL -- the NOEL was calculated from the LOEL?

DR. RUBIN: Yeah.

DR. FUCALORO: By just doing --

DR. RUBIN: No, the NOEL is a determined NOEL. In other words, those animals were actually exposed

at that dose.

DR. FUCALORO: And experienced nothing?

DR. RUBIN: And experienced no observable effects. So that's our NOEL. And that's the NOEL that we're going to calculate our RELs and our MOEs based on. Chronic toxicity. This is an issue, because it's become apparent to us that there is chronic exposure to MITC. It's not included in this document. The data are currently being crunched through at DPR to give us chronic-exposure data.

But with chronic toxicity, we don't have any inhalation experiments. And I understand that probably with -- probably not a very common thing to see chronic-inhalation experimental data. Anyway, but I thought I would flash this slide by just to show you that we do pick up some chronic effects.

We determine NOELs of 10 -- 10 ppm in the water, which is equal to 463 mics per kick per day in a rat study. And 0.4 milligram per kilogram per day in a dog study. Dog study was very problematic, because the animals at the beginning of the study were exposed to huge doses of corn oil, and they were getting sick on the corn oil. So it's not a real clear study to begin with.

But I want to move on from chronic, because we don't really have a study to base anything on there.

Is there a question? Okay. The issue of oncogenicity --

DR. FUCALORO: Wait. I have a question.

DR. RUBIN: Okay.

DR. FUCALORO: Previous slide. Study 1 and Study 2 have essentially the same NOELs and LOELs, don't they?

DR. RUBIN: Yes.

DR. FUCALORO: Did you note that? I'm sorry.

DR. RUBIN: Not only do I note that, but it's interesting to note that those NOELs and LOELs are similar to the subchronic inhalation study.

DR. FUCALORO: And I would point out there was missing, of course, some signs, vomiting, excessive salivation, liquid feces, at -- and the number's missing.

DR. RUBIN: Oh, it -- that's at the LOEL dose.

DR. FUCALORO: Is that the LOEL?

DR. RUBIN: Yeah. At 2.

DR. WITSCHI: Wasn't this on the dog study, the .4 milligram per kilo per day produced some signs of toxicity? That's what it says.

DR. RUBIN: Excuse me?

DR. WITSCHI: At the .4 milligram kilo dog study. You had --

DR. RUBIN: Oh, I'm sorry. I have that wrong. That's a mistake. That should be 2.

DR. WITSCHI: Oh.

DR. RUBIN: That should be 2. It's in the report, sloppily. Okay. Should I move on? Okay. Oncogenicity, MITC does not appear to be oncogenic in any of the three chronic studies where it was looked at. And again, these are oral-exposure studies.

However, I want to bring to your attention that in the two-year rat study, the drinking-water study, there was an apparent increase in multiple benign mammary tumors in terminal survivors. Consideration -- and I have a whole slide of this, if we want to go through this, the numbers.

Consideration of incidence rates for single benign tumors separately and in combination with the multiple benign tumors, as well as the incidence rates for malignant mammary tumors favors the conclusion that the increase in multiple benign tumors was not treatment-related. It did not achieve statistical significance. And basically, there was nothing else going on in the mammary gland with related tumors, single tumor, in decedents, in terminal survivors.

We made a judgment that this was not a treatment-related effect. I want to say in passing,

however, that I have included in this document a draft of the Metam-Sodium risk assessment, which I wrote. And with Metam-Sodium, you do get clear, frank, oncogenicity, but not in the mammary gland. You get blood-vessel carcinomas -- not carcinomas, sarcomas.

And this is something that we should recognize, that the parent compound, but apparently not the daughter compound, is carcinogenic.

DR. BLANC: That was in the same species that the -- these studies were negative with?

DR. RUBIN: In two species, actually. Rats and mice. This one here, this is a rat study with MITC where you get a small blip in mammary.

DR. BLANC: Right. And it was a rat study with the angiosarcoma?

DR. RUBIN: Angiosarcoma, rats and mice.

DR. BLANC: Well, I think it's going to be a problem, and I think it's going to have to be addressed. Because it doesn't -- on the face of it, if it's a compound which is quickly transformed -- that is to say, Metam-Sodium quickly transformed, in an aqueous environment quickly broken down, it's hard to believe that even in the animal studies where Metam-Sodium was associated with angiosarcoma of the liver, it was actually the parent compound that was causing angiosarcoma of the

liver.

So the two sets of findings are inconsistent with each other, unless it's related to one of the other -- well, no. Even so, it would -- you know, it would have to be carcinogenesis-related to hydrogen sulfide or something. It's hard to understand how the two findings --

DR. RUBIN: It is hard. It is very difficult to tease this out.

DR. BLANC: And I think it raises a larger point, which I don't think we can get into today. But which is, that structuring the document as a health assessment of methyl isothiocyanate carries with it a certain problem.

Which is, that the real issue that we're dealing with is Metam-Sodium, and all of its breakdown products, of which methyl isothiocyanate is a prominent, but not the only one. And whether organizing the entire document -- I don't mean organizing, necessarily. But titling it as a evaluation of methyl isothiocyanate, I'm not sure if that's a help or hindrance.

DR. RUBIN: Right.

DR. ATKINSON: The Metam-sodium will not get into the atmosphere.

DR. BLANC: I understand that. But MIC

does.

DR. ATKINSON: Yeah.

DR. BLANC: And the carbon disulfide and the hydrogen sulfide does. And all those are breakdown products. And then if we're dealing with this other product, you also have to think about formaldehyde and -- and other breakdown products as well. So I think it's a real challenge. I'm not quite sure I have a solution to it.

But I see that there's a real problem in the -- I don't know how you're struggling with it with the health effects. But it seems it must be a nightmare.

DR. RUBIN: This is a very sticky one. And it's part of the reason why I decided to include the draft of the Metam-Sodium document, so that it's very clear that we recognize that it's positive for carcinogenicity, the parent compound.

It is not at all clear to me why the daughter compound doesn't register as such. There could be -- there could be any number of explanations. It wasn't stable, it broke down in certain ways. And how we are to assess this in the real world where people are exposed to air levels of MITC, but not to Metam perhaps in the air, that's something I'm willing to take the direction of the panel on how to handle that. That's a

very sticky problem.

DR. WITSCHI: I have a question about those tables. You know, I think you really should treat lumps as lumps. And look again at the tumor data. If you just take total number of lumps, regardless of whether they are benign and malignant, the total numbers of animals that were at risk.

DR. RUBIN: I think I did that.

DR. WITSCHI: Not to -- not this slide. Then when you do this, you find that the guys on the MITC, in all treatment groups, the incidence of tumors higher. Now, whether it would be significant, I don't know.

DR. BLANC: No-treatment group -- the no-treatment group is higher.

DR. WITSCHI: No, the treatment ones. All three treated groups are higher than the controls.

CHAIRMAN FROINES: Where are you reading?

DR. WITSCHI: Can you --

CHAIRMAN FROINES: We have to stop, actually. Let's do this, and then we have to stop. We have to be out of here at 3:45, and we have to finish the RELs.

DR. RUBIN: Okay.

CHAIRMAN FROINES: Go ahead, Peter.

DR. WITSCHI: I should see the bottom.

DR. RUBIN: The bottom is the malignant.

DR. WITSCHI: Okay. See, if you -- if you add up those and those --

DR. RUBIN: Total benign plus total malignant?

DR. WITSCHI: Total benign and total malignant in the ones that died before, and the ones that were cured. Then you have 60 at the bottom. You had 60 animals at risk. And in every single group, the sum of total tumors is higher than was in the control group.

CHAIRMAN FROINES: Thank you very much.

DR. RUBIN: That's it?

CHAIRMAN FROINES: That's it.

DR. RUBIN: Okay.

CHAIRMAN FROINES: Sorry we can't accommodate you further, but we had these other items on the agenda before we found out this was going to be on. Let's go, Melanie. Let's go, folks. We've got to be out of here. At 3:45, we're out.

DR. MARTY: I think all that we're missing for the comments from the panel on the chronic REL document is comments from Dr. Witschi.

DR. FUCALORO: Is he the only -- comments only from --

CHAIRMAN FROINES: Okay. Peter.

DR. WITSCHI: Okay. I -- the first one, chlorinated dibenzo dioxins, and I worked with the panel which reviewed the dioxins assessment of the EPA. And after the EPA had given its presentation, the Chairman asked, "Why does the EPA spend so much effort on dioxin?" And the EPA administrator said, "Well, because we have a large basis of scientific data on dioxin." And in view of those facts, I'm not going to comment on the dioxins. The chloroform, I have a question.

CHAIRMAN FROINES: You've finished dioxins?

DR. WITSCHI: Oh, yeah. I am not going to touch this with a pole.

CHAIRMAN FROINES: Good.

DR. WITSCHI: No way. Okay. In page A-41, chloroform; right?

DR. COLLINS: Uh-huh.

DR. WITSCHI: You have in the second paragraph a human study which showed some effects between 10 and 995 milligrams per cubic meter. Now, if you go to the -- the previous page, then you certainly would have an inserted factor for LOAEL of 10, and an interspecies factor of 10. So you would have an uncertainty factor of 100. The animal in the species falls out; right? Okay.

Then you take the 100 and divide it by 100, and you come up either 10 milligrams per cubic meter, and

divided by 100. And you wind up with the value which is 3 times lower than the one you derived from the animal experiments.

DR. MARTY: Correct.

DR. WITSCHI: Okay. So --

DR. MARTY: Why did we not do that?

DR. WITSCHI: Yes.

DR. MARTY: As I'm recalling -- and I will go back and look. But the Bomski paper and the Phoon paper, part of the issue is, you can't tell who had the liver toxicity -- that the people that had the liver toxicity, what exactly were their exposures. So it's an exposure-uncertainty issue.

But I do agree that that is one thing we should do, is take the bottom end of the range of exposures, make the assumption that that exposure was associated with hepatotoxicity and create a REL.

The fact that it's a little -- it's three-fold lower, but that's actually fairly close agreement, given all the uncertainty. But the reason we didn't focus on that was this exposure issue.

DR. WITSCHI: Well, it's really the question of, if you have human data that are usable, wouldn't we rather use them? I agree it's trivial difference. It's rather question of -- I don't know.

CHAIRMAN FROINES: Your call.

DR. WITSCHI: I'd go with the human data.

DR. COLLINS: I think the other problem we have is that it's jaundice rather than some of the mild effects we deal with. In fact, how do you deal with a seriously adverse effect? We put a hundred false-safety factor instead of a 10?

DR. WITSCHI: Oh, I see. No, no. No, we are talking about interspecies difference. There you have to go by the rules. We have -- in people, we don't assume more than 10. Although, might be, in the case jaundice, a larger factor might be appropriate, because of people could have preexisting liver disease or there is interaction with other things. I don't know.

DR. BLANC: Well, did they -- how did they define jaundice?

DR. COLLINS: I don't know. I really -- I didn't develop -- that's one I have to go back and find.

DR. BLANC: You need to find out. Because if they were -- you could make the -- for people to be clinically jaundiced, they have to have bilirubin that is probably more than twice the upper limit of normal. So you could, you know, put in an added factor for that, and assume that -- in other words, if what they were doing was observe jaundice in humans and not measure bilirubin

abnormalities, you could assume that a level half that amount might cause an elevated bilirubin absent clinical jaundice.

DR. MARTY: There was actually a more significant issue. And that is in both studies, the workers had viral hepatitis. So --

DR. BLANC: Oh, never mind.

DR. WITSCHI: Well --

CHAIRMAN FROINES: That kind of takes out the jaundice.

DR. MARTY: It wasn't sure if it was the cart before the horse. In one of the studies, the authors thought that chloroform exposure was a predisposing factor.

DR. BLANC: To viral hepatitis?

DR. MARTY: To viral hepatitis.

DR. WITSCHI: See, now considering the fact of how much hepatitis is around these days, you might start thinking we are not even a sensitive population, by the guys who have subclinical hepatitis.

DR. BLANC: Well, that's your factor of 10. I think if the studies are that flawed, then you shouldn't use the human studies. But you should have a rationale --

DR. COLLINS: See, the other thing with

Bomski, we have to throw in a factor of 10 for subchronic, was one to four years.

DR. MARTY: We could take another look at the Phoon study. I have read that paper. It's been a long time. But I may be mistaken that they initially thought it was viral hepatitis, and then attributed it to chloroform. I'll go back and look at that Phoon study in '83 and see if it's usable.

CHAIRMAN FROINES: Why don't you go back, look at it, communicate with Peter, and we'll -- we'll basically -- if the panel agrees, we'll agree with the conclusions that you two come up with. I don't think we need to hold this for some sort of meeting at some point. It's not --

DR. FUCALORO: I agree.

DR. MARTY: Okay.

CHAIRMAN FROINES: When it gets to 3:30, everybody will agree to almost anything. I'm getting a little --

DR. FUCALORO: I mean, that was an honest agreement on my part, for the record.

DR. WITSCHI: Okay. Next one? Ethylbenzene. I think on page A-61 I would take issue with the term "subacute developmental toxicity study," because this would imply -- if you say "subacute

developmental toxicity," this would imply there are acute developmental toxicity or chronic developmental toxicity. This doesn't exist; okay? But that's a trivial point.

DR. COLLINS: I thought just cross the word out.

DR. WITSCHI: That's a trivial point. My question is -- and I don't know if that's come up before. On page 60, third paragraph from the bottom, you have what looks like a perfectly well-designed study for -- for a subchronic study; right?

DR. COLLINS: Weeks, yeah.

DR. WITSCHI: Yeah.

DR. FUCALORO: Is this Clark?

DR. WITSCHI: That's Clark.

DR. COLLINS: At least through the comparison, we could do that --

DR. WITSCHI: So then, I was wondering when -- then going with the developmental study is the right thing to do.

DR. COLLINS: One thing I'd like to say, we are going back and looking at everything. This is an EPA RFC. We're going back and redoing them by our own methodology based on what the panel said. And I think this would be to see whether the developmental study agree well, for instance, doing our analysis on the Clark study,

do they agree or not. And as one method, to see whether the thing is an outlie or whether it agrees with the other data.

DR. MARTY: We also looked at the NTP bioassay. And it -- it has some information, but it's a little hard to interpret. But if you look at that bioassay, and also the subchronic study -- but that was done by NTP prior to the bioassay. The numbers actually are in fairly reasonable agreement with the REL we developed from the developmental text. We can actually insert that information into the text, so it's clear.

DR. WITSCHI: Well, yes. Again, I was wondering, because a developmental toxicity studied in rats, kind of a special case. It's a question of principle, again. Whether you go for something which would be your run-of-the-mill toxicity study or whether you are going for this, a rather special case. Because many things which show up in developmental toxicity studies in rats are not really too relevant for a human situation, if I am correct.

DR. BLANC: Why would you be correct? Why would that be correct?

DR. WITSCHI: Well --

DR. BLANC: I think it's more of an example that, by chance, they happen to have a more sophisticated

study with subtler end points for analysis. Take lead, for instance. Would you -- you know a lot about lead. If I have a developmental study in rats that show the effects of lead, I'd say it's very relevant.

DR. WITSCHI: I'd say it depends on what you looked at in rats.

DR. BLANC: Their SAT scores.

DR. COLLINS: What's the rat population here at the colleges?

DR. FUCALORO: You're looking at them.

DR. BLANC: I mean, I'm not sure there's a general principle there.

CHAIRMAN FROINES: Where are we on this issue?

DR. COLLINS: Where on this? That we've based on a developmental study, we'll go back and make some comparison, using some of the other studies and see how well they agree. And then decide whether we have -- we can find out -- we have an outlier with the developmental study. Then maybe we are going to have to --

DR. WITSCHI: Well, first of all, I would take issue with this developmental studies. Because in the rat study, as described, you have control toxicity. And we now know these days, if you have a maternal

toxicity, forget about it. That's not relevant. So that was one of the reasons why I questioned why taking the -- not looking at the rat study. Because I think that's pretty well-established, maternal toxicity is a no-no with teratology study.

DR. MARTY: I think that there's maternal toxicity in the rats, but not the rabbits in that study. We had the same NOAEL. So I think, you know, we always get heart burn about using numbers where you have maternal toxicity, because of that whole issue.

But one of the reasons we thought it was okay to use this, is because there was also the decreased live kits in the rabbits that were exposed to the same concentrations. In fact, it was the same study. And it was also the NOAELs is supported by Clark when you do that calculation.

So I do agree that there are uncertainties using, first of all, the developmental studies for chronic end points. Although, we have concerns that if you do that in your REL is much lower than any other study that you use, are you protecting against developmental effects. So we have that concern. And that's why we have opted in some cases to use developmental studies.

CHAIRMAN FROINES: Yeah. Except I would almost argue -- we've had this discussion before. I would

almost argue that you should have a category for developmental studies and that -- keep that separate from a classic chronic toxicity. Because it is a case in and of itself, so to speak.

We've had that discussion. Because the time frame of the developmental studies is different than what we normally think about. So we're also into the issue of averaging. I should say, by the way, he said something that made me nervous. I don't -- yeah, I don't want to be taking up compounds and taking this panel's time if you are in the process of reviewing those compounds. Because you want to have a state RIR versus a EPA.

We should get to it when you get to where you need to go. We shouldn't be -- I really don't want a hundred and twenty compounds coming back to me that you've now got new RELs for and have to redo this whole process. I mean, everybody will quit.

DR. MARTY: What we've done is we've -- we are responding to --

DR. BLANC: Your request.

DR. MARTY: -- to the previous instruction from the panel to go back.

CHAIRMAN FROINES: I understand that. But that means that, if we have compounds that we're doing, and you've got at least 80 more compounds to give us;

right? We've only gotten 40. We've got 80 to go.

DR. BLANC: John, John, for these first 40, one of our comments was, we wanted them to go back on certain ones. And that's what they're doing.

CHAIRMAN FROINES: I'm not talking about that. I'm simply saying, he said, "We're looking at all the compounds that are EPA documented to develop our own RELs." And I'm simply saying, for the next 80 compounds, subtract out the ones that are EPA that you're re-looking at, and don't bring them forward until you're ready.

DR. MARTY: Yes, we don't intend to bring them forward until we've done that.

DR. WITSCHI: Go on? Okay. Hydrogen sulfide. The only thing I have, Andy Rubin's assay at the end of his presentation of some values, just make sure that they are about the same, you know, between the two agencies. Okay.

CHAIRMAN FROINES: Realize, everybody, that the levels of -- never mind.

DR. WITSCHI: No, I know.

CHAIRMAN FROINES: Of H2 is that of being reported with MITC exceed their realm.

DR. MARTY: Exceeds our proposed realm.

DR. WITSCHI: Okay. The last one I have is

methyl chloroform. And if you look through these data, the way I -- they are described, the gerbil is more sensitive as man; right? And then you take the gerbil data and still build in the interspecies factor of 10 in an example where man is definitely less sensitive than the test animal was.

You have -- on page A-158, you have some of NOELs for men, 250 ppm, hundred and -- 345 ppm, 350 ppm, almost. And the gerbil is much lower. And yet you introduce the factor of 10. It doesn't make sense, to some extent.

DR. MARTY: Well, I think we were concerned about the quality of the data that came out of the human studies, whether they could actually have found a neurological effect. There were also case studies which are not usable in quantitative risk assessment, but that indicated that methyl chloroform is capable of producing neurotoxicity in humans.

DR. WITSCHI: I have problems, in view of data, where man seems to be five times more sensitive than the gerbil, to take the gerbil and make man ten times more sensitive.

DR. MARTY: Well, I guess the only thing I would argue, I'm not convinced that humans are much less sensitive than gerbils, by looking at the information that

we have, which isn't very strong. It would take more than that to convince me.

DR. WITSCHI: Okay. We have this study on page 158. One, two, third paragraph from top. 250 ppm, no changes, exposed for more than one year, 150 workers. Then --

DR. MARTY: That was cardiovascular, Kramer. Am I looking at the right one?

DR. COLLINS: Yeah, yeah.

DR. WITSCHI: Then one down, we have 22 female workers, hundred ten received -- had a ppm 6.7 years. Failed to identify neurotoxicity. I mean; okay. What's wrong with those data? At least the way they are presented here, nothing.

DR. MARTY: Well, I can go back and look at those studies, but I'm -- I'm certain that the person who wrote this, the reason they didn't want to use Maroni at all, they didn't have a lot of confidence in the study. The fix would be to go back and look at it and also to explain why we're concerned about using that study.

DR. WITSCHI: Well, and see -- then the gerbil, you take a neurological end point, astrogliosis, a-s-t-r-o-g-l-i-o-s-i-s, so -- okay. I mean --

CHAIRMAN FROINES: It seems to me that the -- Peter's right, that the automatic adoption of

ten-fold safety factor, irrespective of the data, is something we need to avoid.

DR. COLLINS: We had an additional problem here. We couldn't use the EPA's RGDR factor, because there was not enough data on gerbils to do it. Otherwise, this could have been a 3.

DR. MARTY: The interspecies --

DR. COLLINS: Interspecies factor.

DR. MARTY: Would have been a 3 if we'd done --

DR. COLLINS: But there's no basis on which to do an OGC calculation on gerbil.

DR. MARTY: Another thing we could do is look again at the body of Maroni and other studies. And if it really appears that way, we can use the Rosengren study in gerbils, but don't include the interspecies factor, if that makes sense.

DR. WITSCHI: Now, the thing with man being ten times more sensitive than the most sensitive species, that's a notion that goes back to about 1910. But I do not think that it's really true. Actually, I find man is remarkably resistant to quite a few things. So --

CHAIRMAN FROINES: I have a question. With this information -- by the way, the senior author on this paper is a fellow named Foa, F-o-a, who's quite a good

investigator. So it seems to me that this burden to demonstrate why this study isn't appropriate. The second question I had, was --

DR. MARTY: Dr. Froines, I don't know where you are.

CHAIRMAN FROINES: I'm talking about the Maroni study.

DR. MARTY: Okay.

CHAIRMAN FROINES: Senior author -- last author is F-o-a, and I know him. Now, the next paper down I'm confused about, because that's the paper that the first author is Mattson. And I may be missing it, but I don't see it in here. Can you help me find it? I'm sure it's me. I don't see it.

DR. COLLINS: It's on page A-159, the third paragraph.

"No evidence of peripheral neuropathy or other neurotoxicity was detected in rats exposed to 200, 620 or 2,000 ppm methyl chloroform six hours per day, five days a week for 13 weeks."

CHAIRMAN FROINES: Yeah, I got it. I'm sorry. Now, that's a very good group of investigators.

DR. COLLINS: That would have a 2,000 ppm NOEL.

DR. WITSCHI: That's actually referenced is

Spencer -- it's a C, not an S -- in the Mattson reference, I guess.

CHAIRMAN FROINES: Peterson.

DR. MARTY: Oh, Spencer's name is misspelled. Oh, yeah. Sorry. Well, what we try to do, if you have animal studies that are conflicting, and you have evidence of an effect in one species but not another, we would take the more sensitive species to use in the case of people. Because, you don't know where humans are on the sensitivity scale. So that's, you know, something that we've always done.

DR. WITSCHI: Well, that was my point with this particular -- I thought we knew where humans are on the sensitivity scale.

DR. MARTY: I guess knowing is a comfort, you know. There's a comfort level there issue. But I'm happy to go back and look at Maroni, and anything else we can find to see if that's the case. And then if it is, what interspecies uncertainty factor, if any, needs to be applied.

DR. WITSCHI: Well, that's what I had to say.

DR. COLLINS: Thank you.

CHAIRMAN FROINES: And you did it with two minutes to spare. You're the first person today to come

in under the time line.

DR. WITSCHI: I'm Swiss.

DR. FUCALORO: Well, he sure clocked you.

DR. WITSCHI: I believe in running trains on time.

CHAIRMAN FROINES: And my watch is two minutes fast, so I think you're five minutes ahead. Can I -- can somebody -- I'd entertain a motion. Shall we adjourn?

DR. BLANC: I make the motion that we adjourn.

DR. FUCALORO: Second.

CHAIRMAN FROINES: All in favor?

THE PANEL: Aye.

(Thereupon the Scientific Review Panel meeting was adjourned at 3:39 p.m.)

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STATE OF CALIFORNIA

I, Kathleen Knowlton, CSR No. 11595, a Certified Shorthand Reporter in and for the state of California, do hereby certify:

That the foregoing proceedings were taken down by me in shorthand at the time and place named therein and were thereafter transcribed under my supervision; that this transcript contains a full, true and correct record of the proceedings which took place at the time and place set forth in the caption hereto.

I further certify that I have no interest in the event of the action.

EXECUTED this ____ day of _____, 1999.

_____
Kathleen Knowlton